ROLE OF MACROPHAGES & LYMPHOCYTES IN RENAL INJUIRY

By

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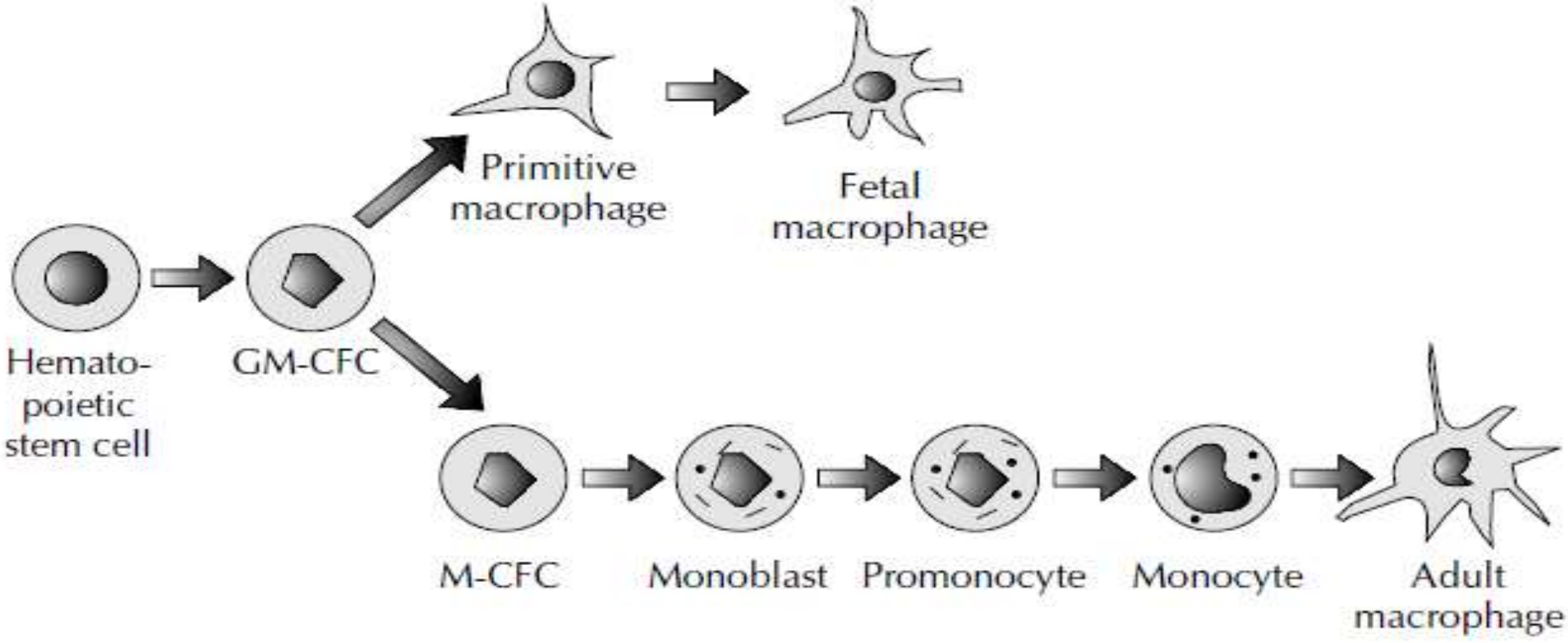
PHASES OF KIDNEY DISEASES

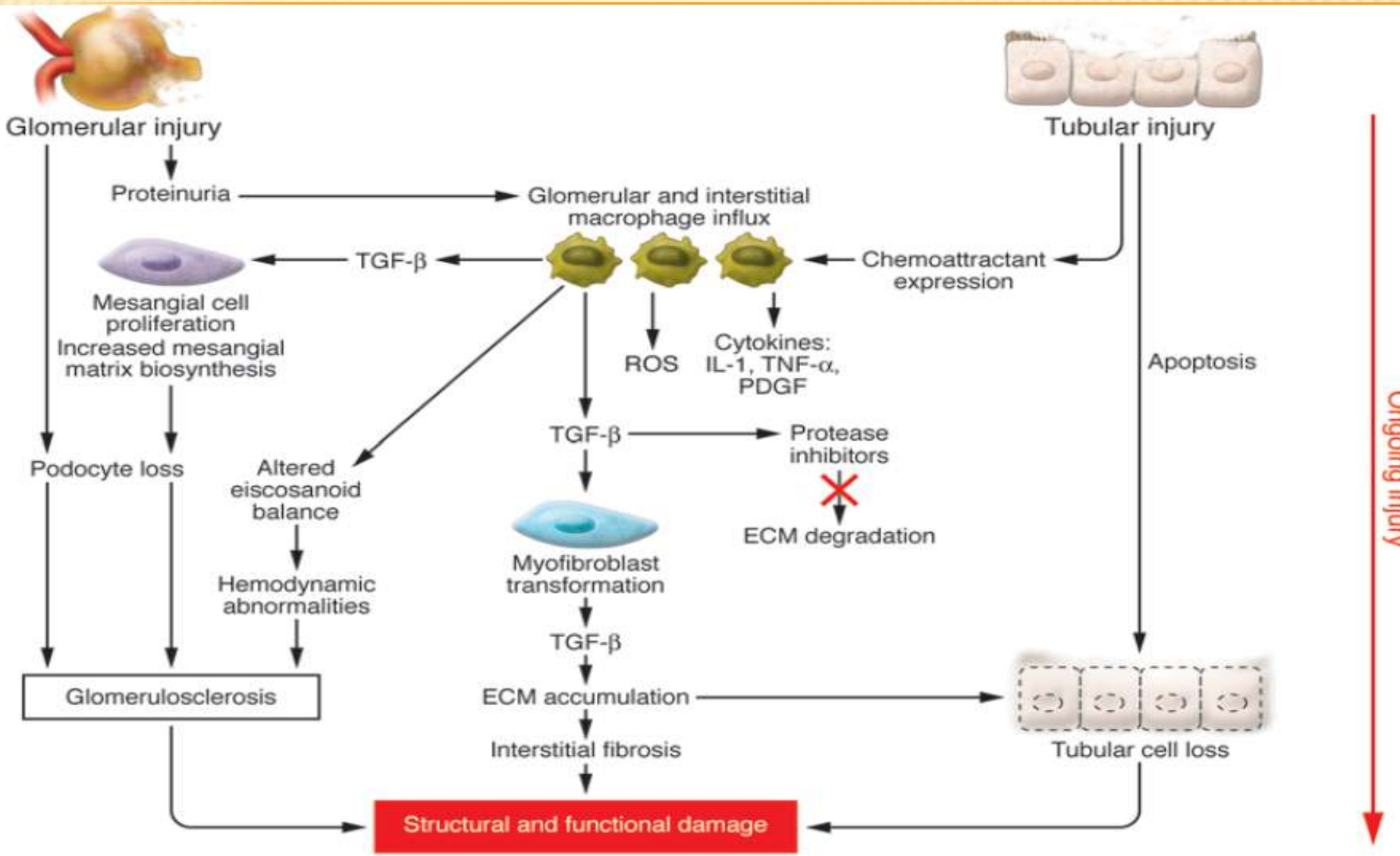
- Injury phase : tissue inflammation
- Reparative phase: development of fibrosis
- Regenerative Phase: proliferation of new cells, derived from either resident cells and/or bone marrow-derived (BMD) cells.

MACROPHAGES

- Diverse and dynamic population of cells
- Perform a wide range of critical functions
- Secrete a wide range of inflammatory factors.



ROLE OF MACROPHAGES IN RENAL INJUIRY



Ricardo SD et al, *J. Clin. Invest. 118:3522–3530 (2008)*

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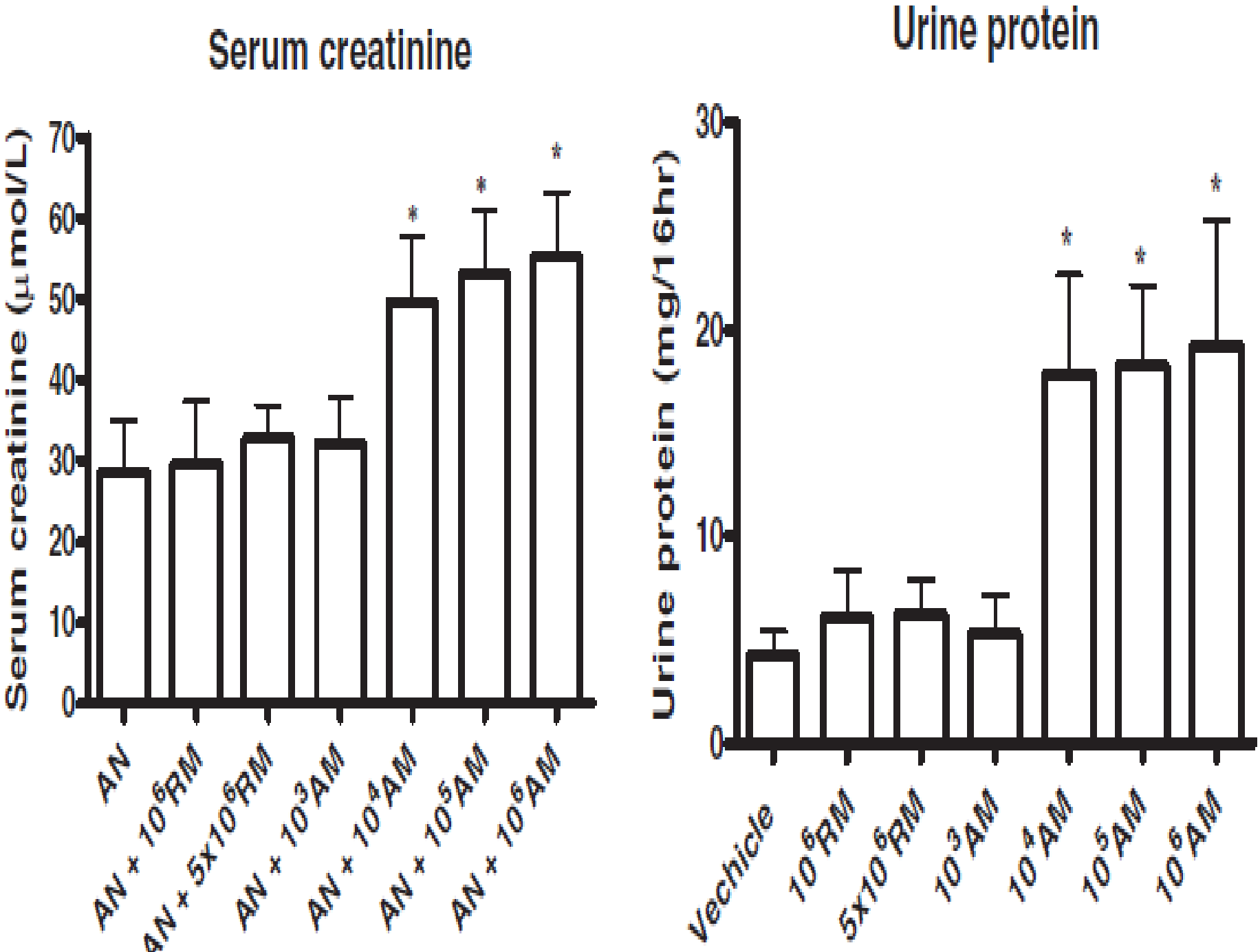
Cardiovascular, Pulmonary and Renal Pathology

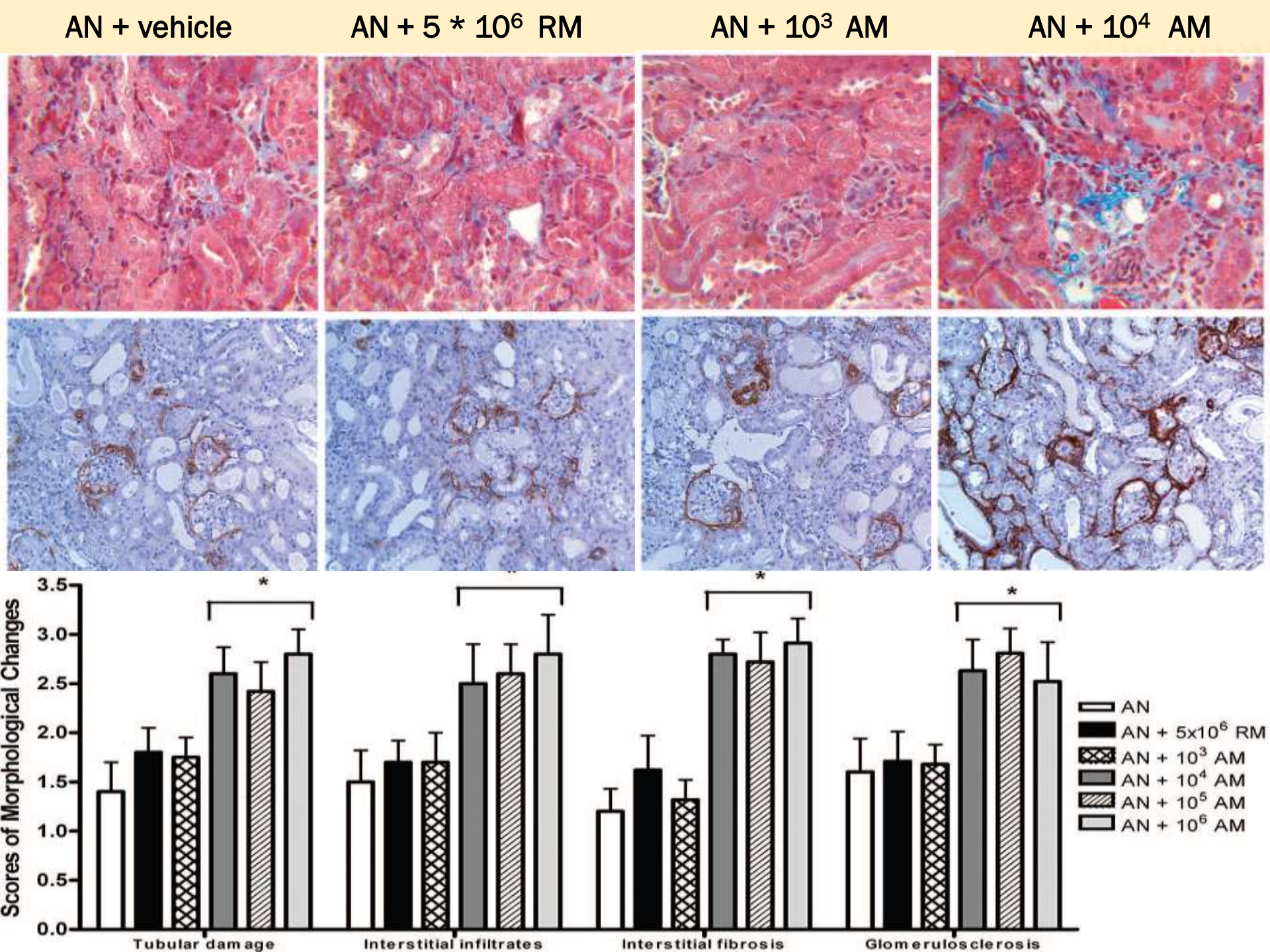
By Homing to the Kidney, Activated Macrophages Potently Exacerbate Renal Injury

Ying Wang,* Yiping Wang,* Qi Cai,*
Guoping Zheng,* Vincent W.S. Lee,*
Dong Zheng,* Xiaomei Li,† Thian Kui Tan,*
and David C.H. Harris*

From the Centre for Transplantation and Renal Research, The University of Sydney at Westmead Millennium Institute, Westmead, Sydney, Australia; and the Department of Rheumatology and Immunology,† Anhui Medical University at Provincial Hospital, Hefei, Anhui, People's Republic of China*

SCID mice with adriamycin nephrosis, an experimental model of human FSGS were treated intravenously with either resting ($1 * 10^6$ to $5 * 10^6$) or activated ($1 * 10^3$ to $1 * 10^6$) macrophages on day 6 post adriamycin administration, and the effects on kidney injury were examined after 28 days.


Serum creatinine
Serum creatinine (μmol/L)
0
10
20
30
40
50
60
70
*
*
*
AN
AN + 10⁶RM
AN + 5x10⁶RM
AN + 10³AM
AN + 10⁴AM
AN + 10⁵AM
AN + 10⁶AM
Urine protein
Urine protein (mg/16hr)
0
10
20
30
*
*
*
Vechicle
10⁶RM
5x10⁶RM
10³AM
10⁴AM
10⁵AM
10⁶AM


AN + vehicle
AN + 5 * 10^6 RM
AN + 10^3 AM
AN + 10^4 AM
Scores of Morphological Changes
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
*
*
*
*
Tubular damage
Interstitial infiltrates
Interstitial fibrosis
Glomerulosclerosis
AN
AN + 5x10^6 RM
AN + 10^3 AM
AN + 10^4 AM
AN + 10^5 AM
AN + 10^6 AM

DOES MACROPHAGES HAVE ANY ROLE IN RENAL REPAIR ?????????

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Adoptive transfer of macrophages ameliorates renal fibrosis in mice

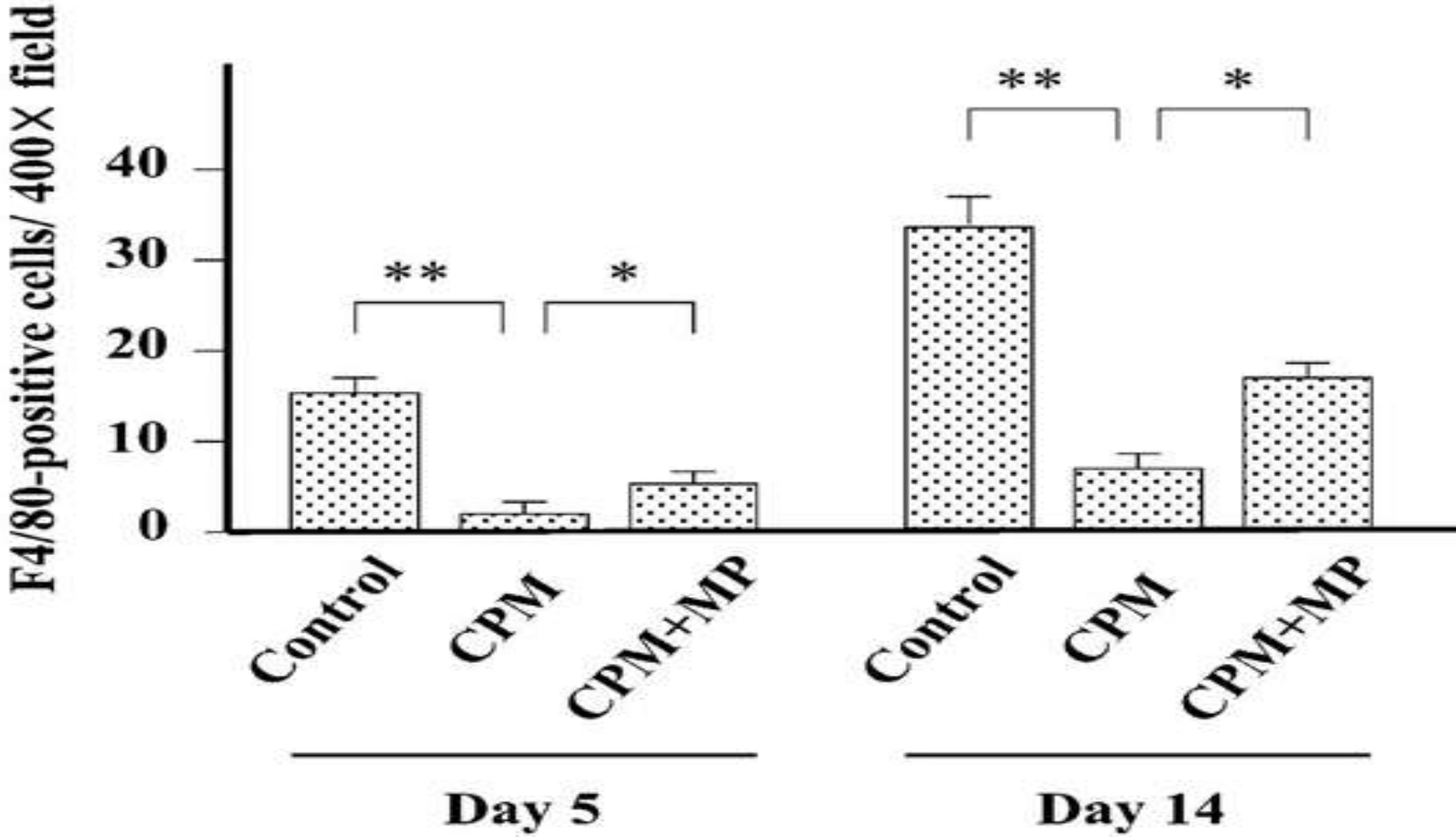
Masashi Nishida *, Yasuko Okumura, Shin-ichiro Fujimoto, Isao Shiraishi, Toshiyuki Itoi, Kenji Hamaoka

Department of Pediatric Cardiology and Nephrology, Kyoto Prefectural University of Medicine Graduate School of Medical Science, Kyoto, Japan

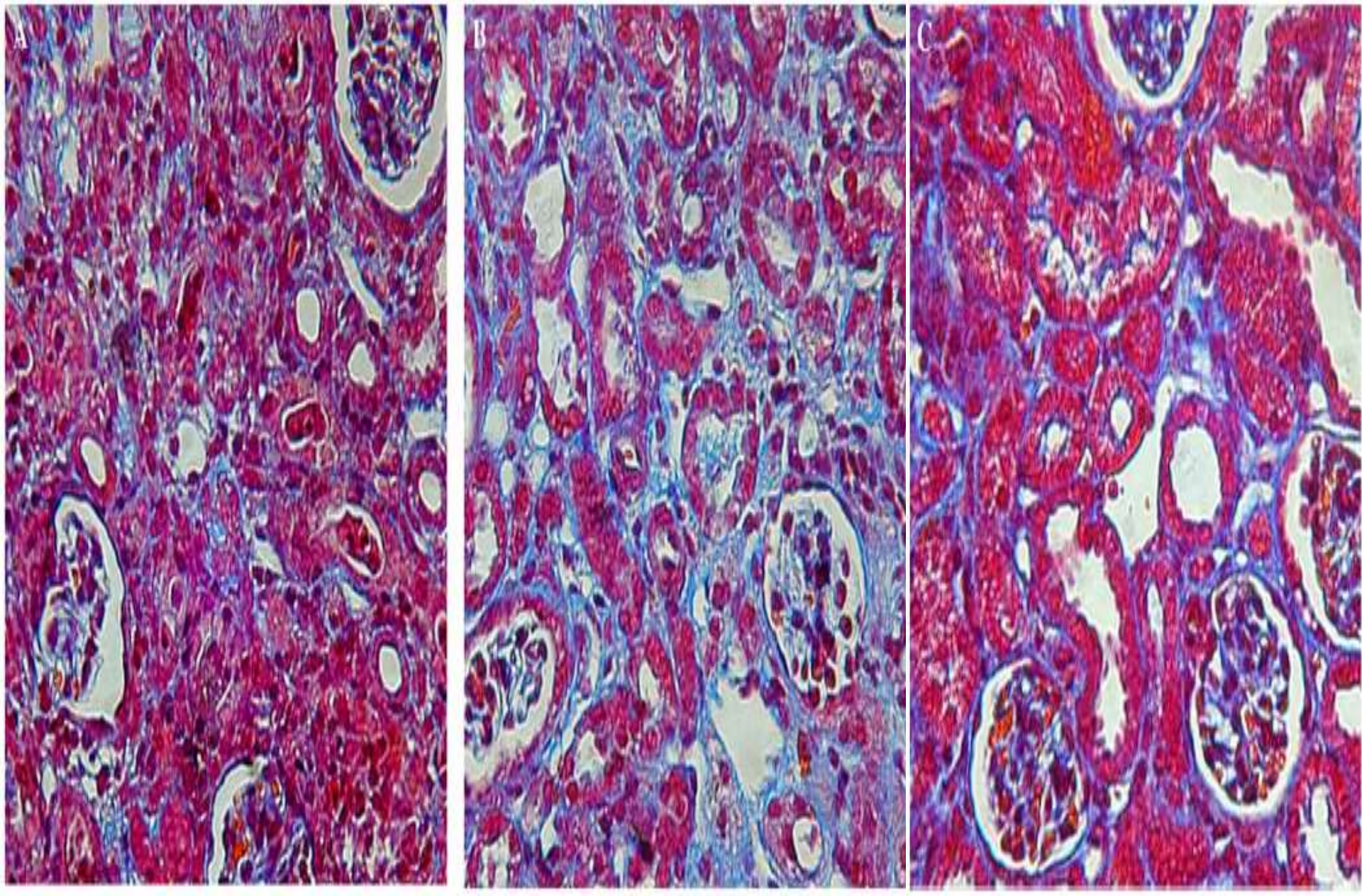
Received 12 April 2005
Available online 26 April 2005

Adoptive transfer of bone marrow-derived (BM) macrophages following pharmacological depletion of leukocytes by CPM in a C57BL/6 mice model of unilateral ureteral obstruction (UUO) and examination at 5, 14 days.

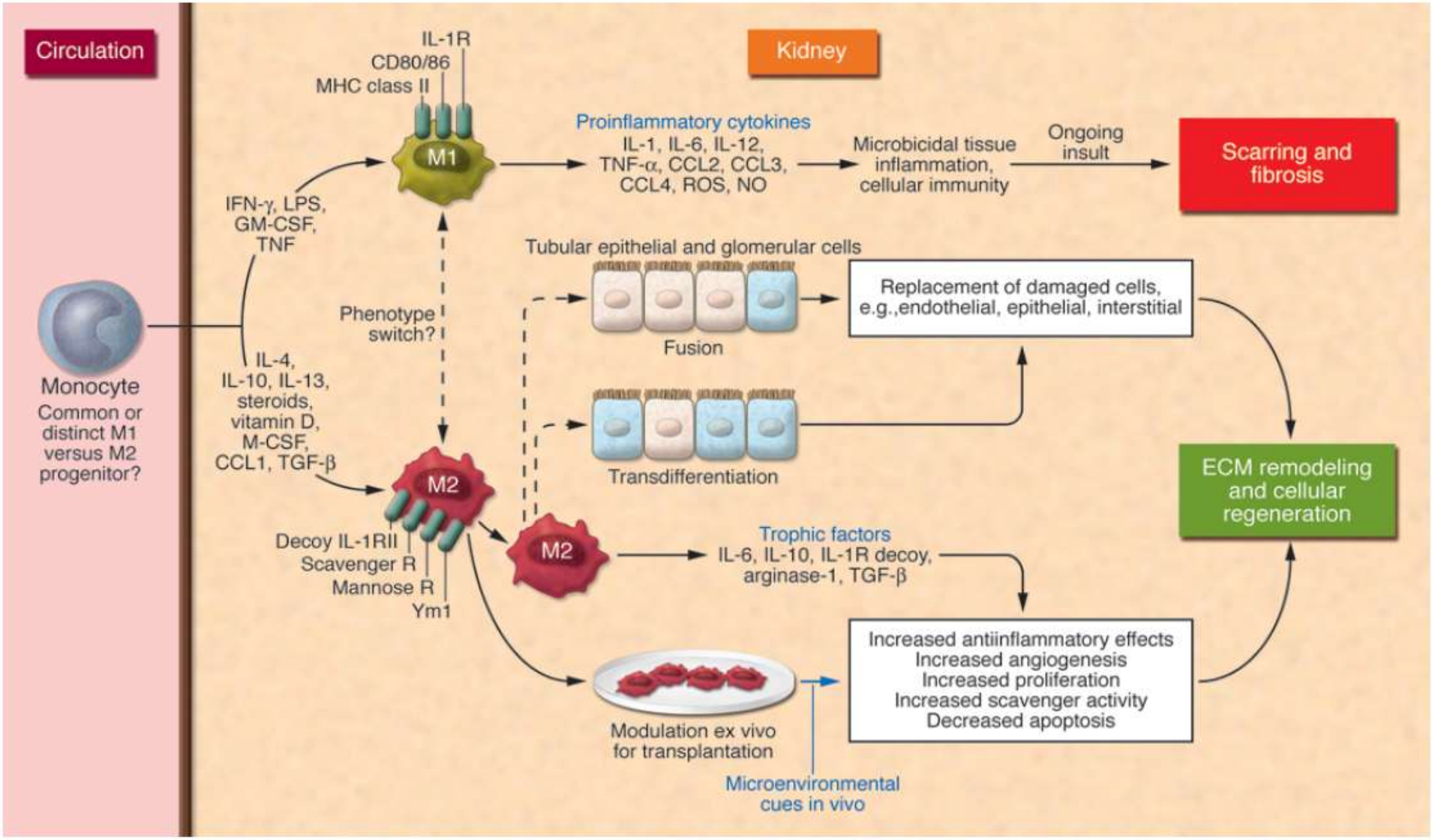
MACROPHAGES INFILTRATING TO THE INTERSTITIUM



Control CPM CPM + MP



ROLE OF MACROPHAGES IN RENAL REPAIR



Ricardo SD et al, *J. Clin. Invest. 118:3522–3530 (2008)*

MACROPHAGE PHENOTYPE

Macrophage activation states and functions

Macrophage phenotype	Activation state	Stimuli	Phenotypic function	Cytokine and inflammatory profile	Unique surface markers
M1	Classical activation	IFN-γ + LPS, TNF, GM-CSF, TLR/IL-1R ligand	Proinflammatory Th1 response	IL-1, IL-12, IL-15, IL-18, IL-23, TNF-α, IL-6, MCP-1, CCL2, CCL3, CCL4, CCL20/MIP-3a ROS, NO, iNOS, NOS2	CD86, CD80, MHC class II^{hi}, IL-1R, IL-12^{hi}, IL-23^{hi}, IL-10^{lo}
M2	Alternate activation (M2a polarization)	IL-4 or IL-13	Th2 responses, type II inflammation	Fibronectin, BIG-H3, arginase-1, TNF-α, IL-6, IGF, CCL13/MCP-4, CCL22, CCL18, β2 integrins	Mannose receptor, scavenger receptor, MHC class II^{hi}, decoy IL-1R11, FIZZI/Ym-1
	Type II activation (M2b polarization)	Immune complex + TLR/IL-1R ligands	Immunoregulation, Th2 activation	IL-10, TNF-α, IL-1, IL-6, IL-12, SPHK1, CCL1	CD86, MHC class II^{hi}, IL-10^{hi}, IL-12^{lo}
	Deactivated (M2c polarization)	IL-10, TGF-β, glucocorticoids	Immunosuppression, matrix remodeling, tissue repair	IL-10, IL-1β, IL-6, TGF-β, ECM proteins, CCL16, CCL18, arginase-1	SLAM (CD150), mannose receptor, MHC class II^{lo}

BIG-H3, fasciclin domain 4 protein; MIP, macrophage inflammatory protein; SLAM, signaling lymphocytic activation molecule; SPHK1, sphingosine kinase 1. Note that *FIZZI* and *Ym1* gene expression is characteristic of the alternative pathway of macrophage activation.

Wang & Harris, *J Am Soc Nephrol* 22: 21–27, 2011.

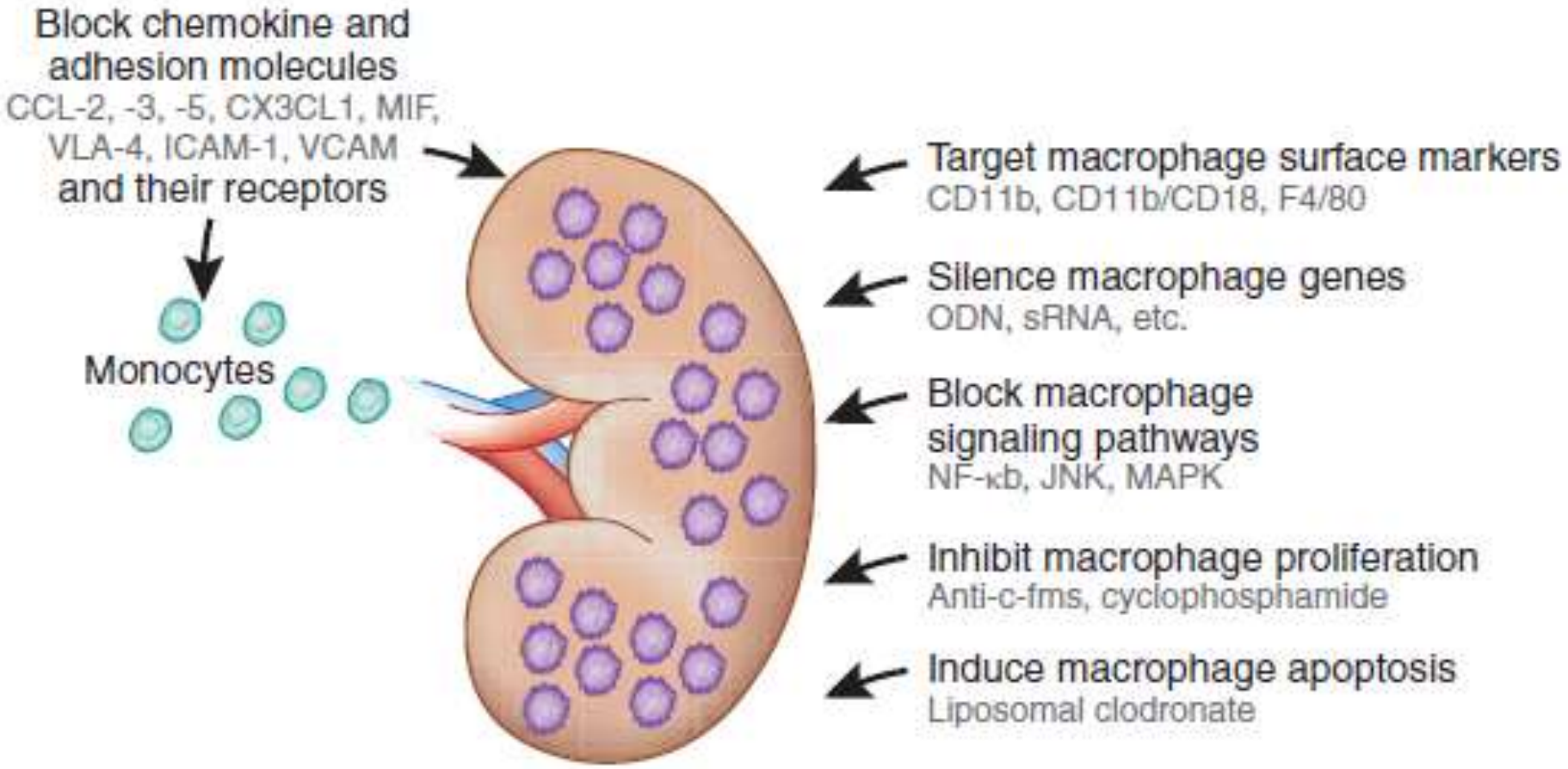
MACROPHAGE STRATEGIES FOR TREATING RENAL DISEASE

Method	Animal Model
A. Macrophage As Target	
antimacrophage sera	Anti-GBM disease (rabbit)
ED7 antibody	AN (rat)
anti–*c-fms*	UUO (rat); diabetic nephropathy (db/db mouse)
liposomal clodronate	Anti-GBM disease
CD11b-DTR	Crescentic glomerulonephritis (mouse)
anti-CX3CR1	Crescentic glomerulonephritis (WKY rat)
anti-CCL2	Anti-GBM disease (rat and WKY rat); crescentic nephritis (mouse); anti-thy 1.1 nephritis (mouse)
CCL2 and CCL5 DNA vaccine	AN (rat)
modified CCL2 DNA vaccine	AN (rat)
anti-CCL5	Anti-thy 1.1 nephritis (mouse); nephrotoxic nephritis (mouse); immune-complex nephritis (mouse)
anti–ICAM-1, anti-CD18	Nephrotoxic nephritis (WKY rat)
NF-κB decoy ODN	Crescentic glomerulonephritis (rat)
ICAM-1 ODN	Renal ischaemia-reperfusion injury (rat)
CCL2 spiegelmers	Alport nephropathy (mouse)
B. Macrophage As Tool	
alternatively activated macrophages (M2a)	AN (mouse) STZ-induced DN (BALB/c and eNOS$^{-/-}$ mouse)
alternatively activated macrophages (M2c)	AN (mouse)
IL-1ra transfected macrophages	Anti-GBM disease (rat); UUO (rat)
IL-4 transfected macrophages	Nephrotoxic nephritis (rat)
IL-10 transfected macrophages	Nephrotoxic nephritis (rat)
macrophages transduced with IκB	Nephrotoxic nephritis (rat)

AN, adriamycin nephropathy; DN, diabetic nephropathy; UUO, unilateral ureteral obstruction; WKY, Wistar-Kyoto.

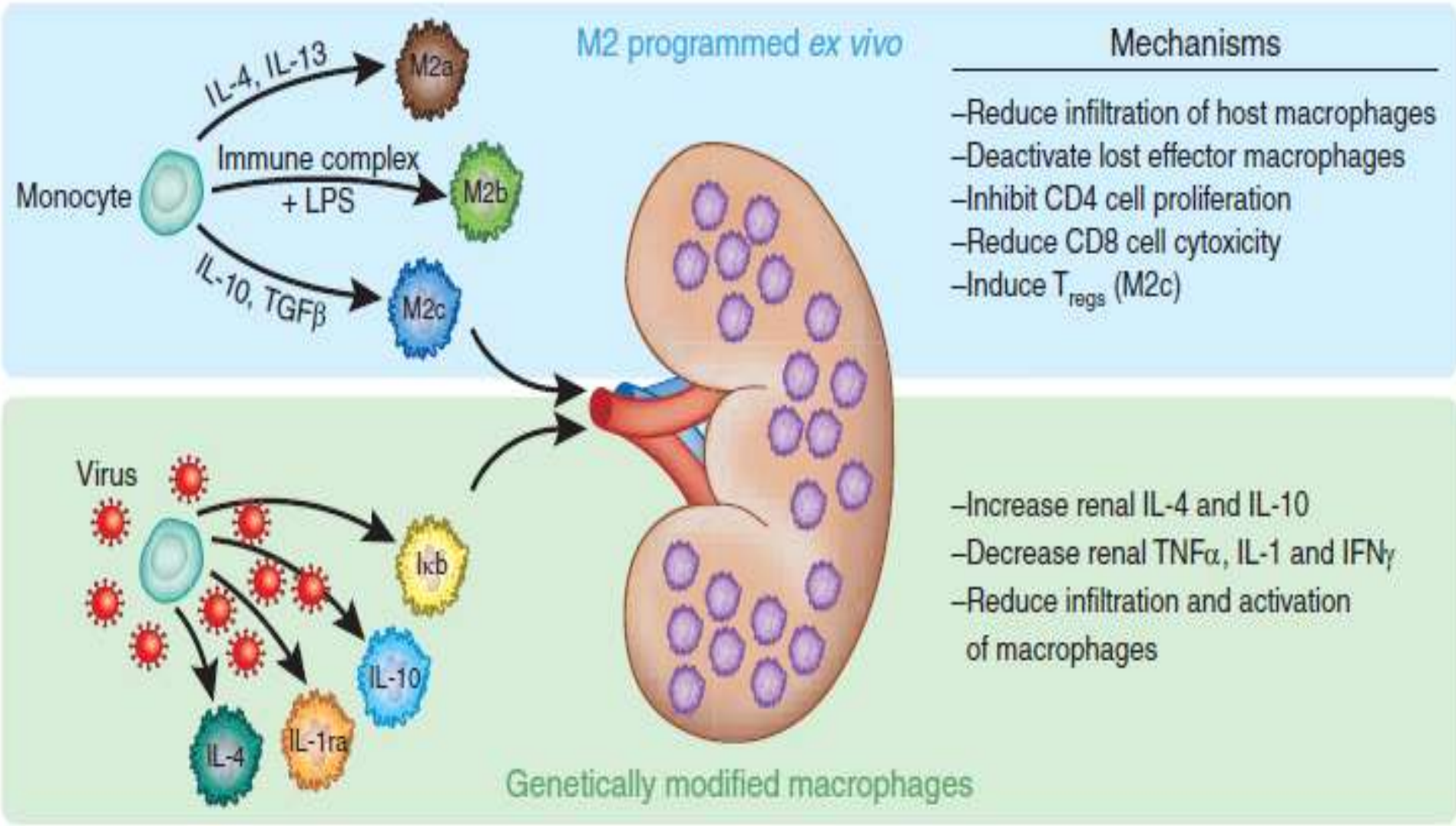
Wang & Harris, *J Am Soc Nephrol* 22: 21–27, 2011.

MACROPHAGES AS A TARGET



Wang & Harris, *J Am Soc Nephrol* 22: 21–27, 2011.

MACROPHAGES AS A TOOL



Wang & Harris, *J Am Soc Nephrol* 22: 21–27, 2011.

1. Wound-healing (IL-4/IL-13 Stimulated) (M2a) Macrophages In Adriamycin Nephropathy

original article

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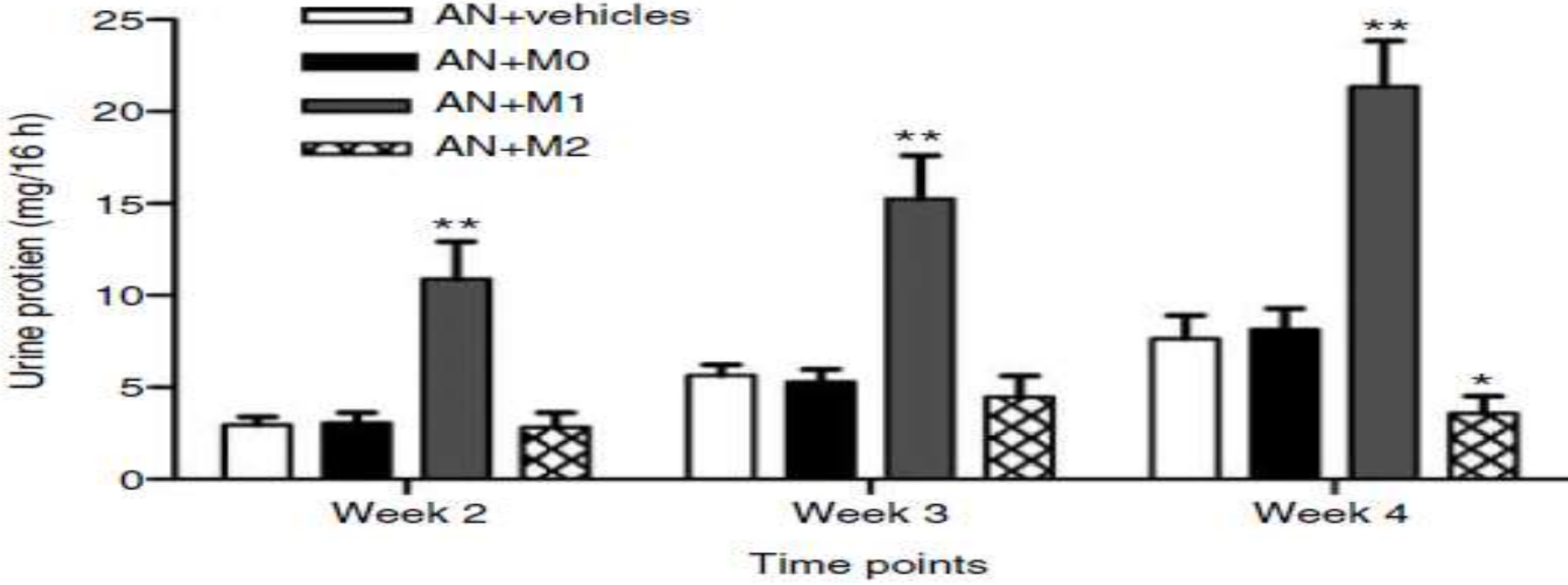
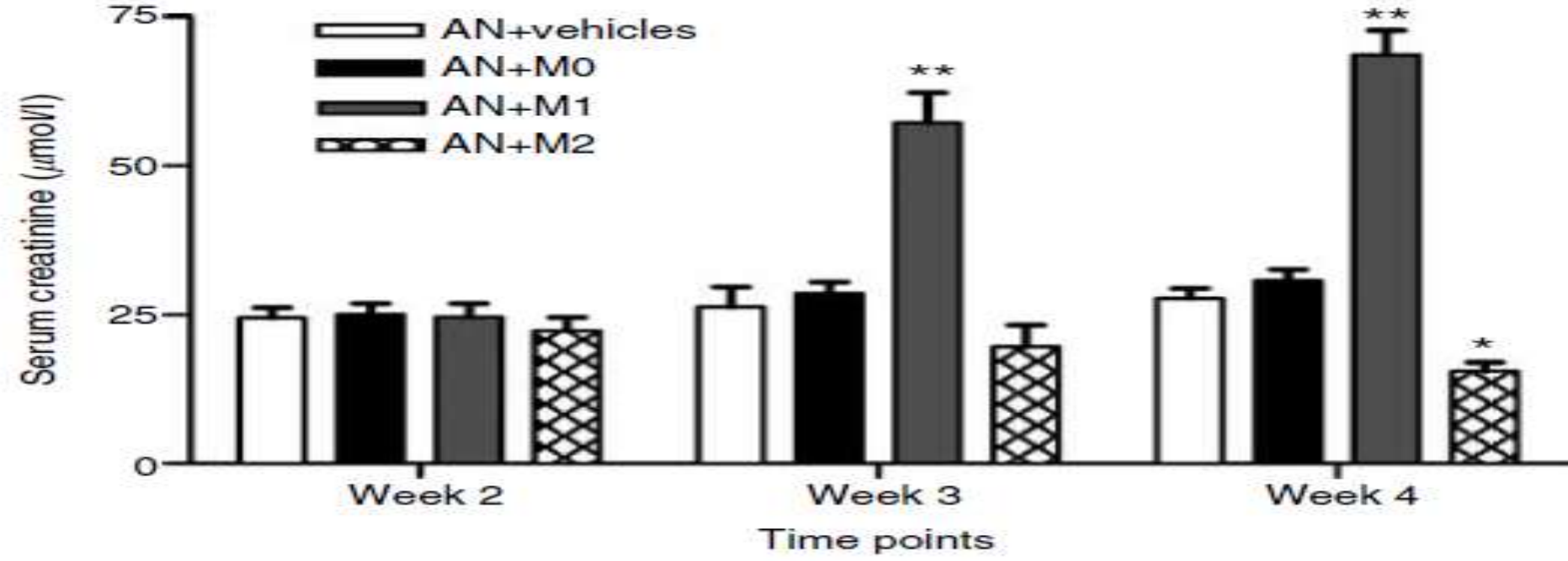
Ex vivo programmed macrophages ameliorate experimental chronic inflammatory renal disease

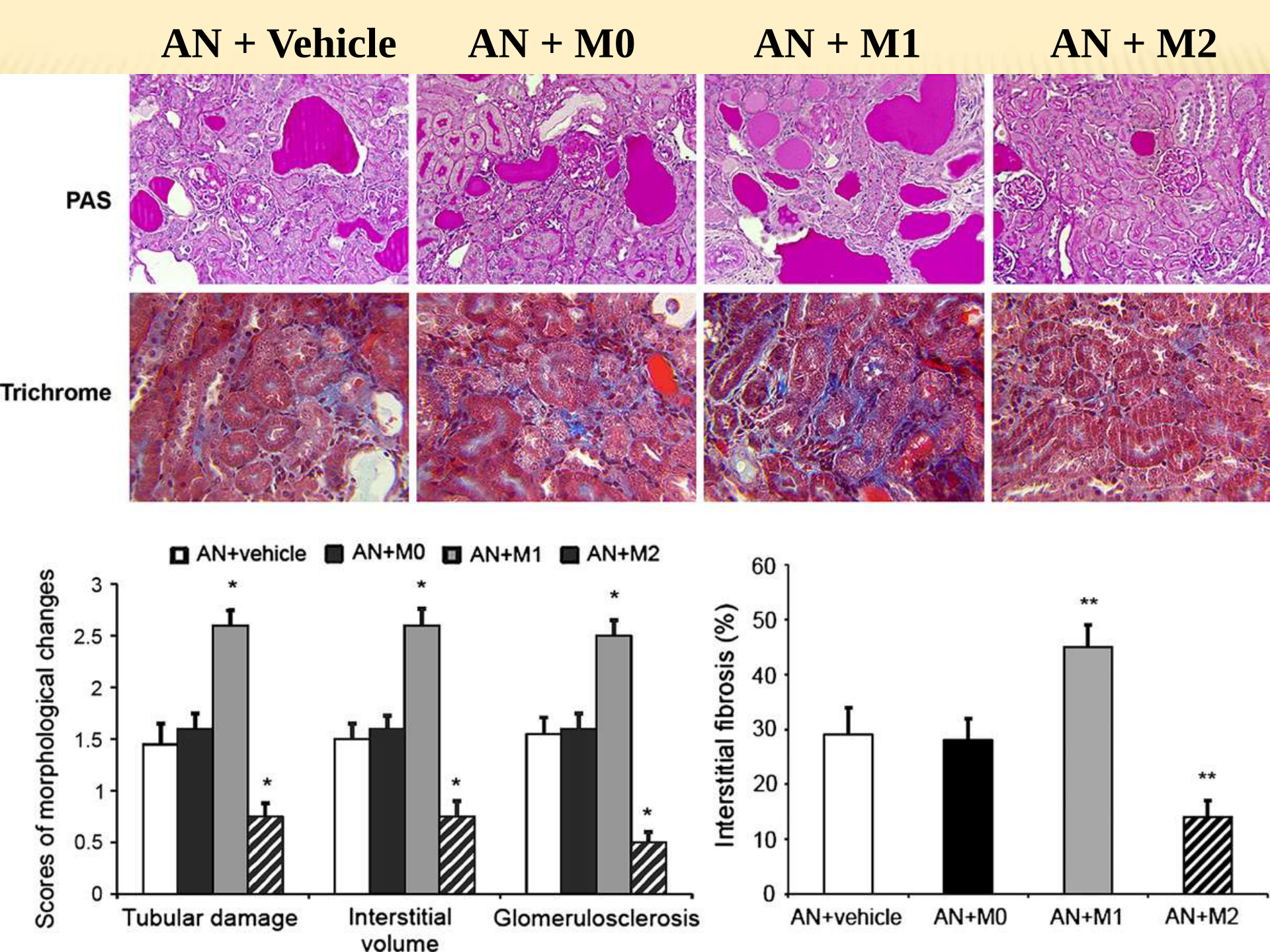
Y Wang[1], YP Wang[1], G Zheng[1], VWS Lee[1], L Ouyang[1], DHH Chang[1], D Mahajan[1], J Coombs[1], YM Wang[2], SI Alexander[2] and DCH Harris[1]

[1]*Centre for Transplantation and Renal Research, The University of Sydney at Westmead Millennium Institute, Westmead, New South Wales, Australia and* [2]*Centre for Kidney Research, The Children's Hospital at Westmead, Westmead, New South Wales, Australia*

Macrophages were isolated from the spleens of BALB/c mice and stimulated with lipopolysaccharide to induce M1 macrophages or with interleukin-4 (IL-4) and IL-13 to induce M2a macrophages. These macrophages were then infused into SCID mice with adriamycin nephropathy and examined after 2,3,4 weeks.

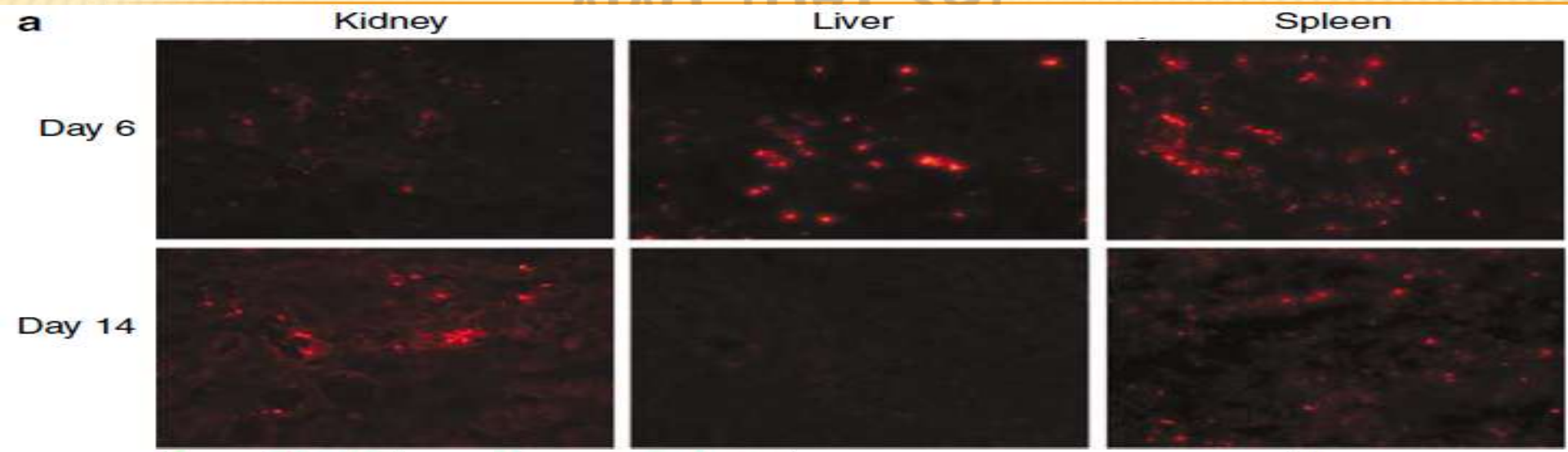

AN+vehicles
AN+M0
AN+M1
AN+M2
Urine protien (mg/16 h)
25
20
15
10
5
0
**
**
**
*
Week 2
Week 3
Week 4
Time points

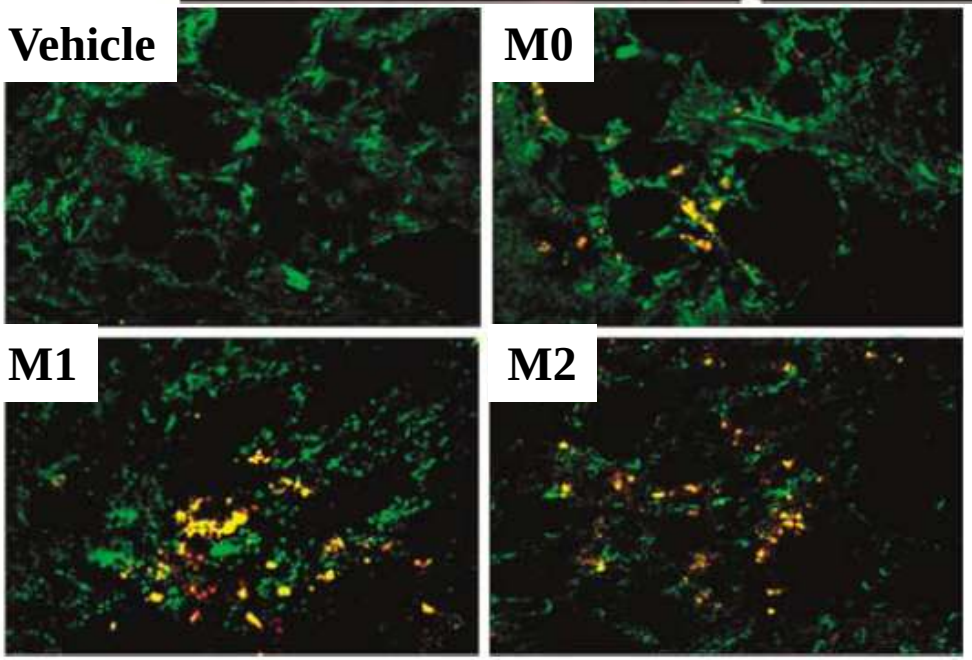

AN+vehicles
AN+M0
AN+M1
AN+M2
Serum creatinine (μmol/l)
75
50
25
0
**
**
*
Week 2
Week 3
Week 4
Time points

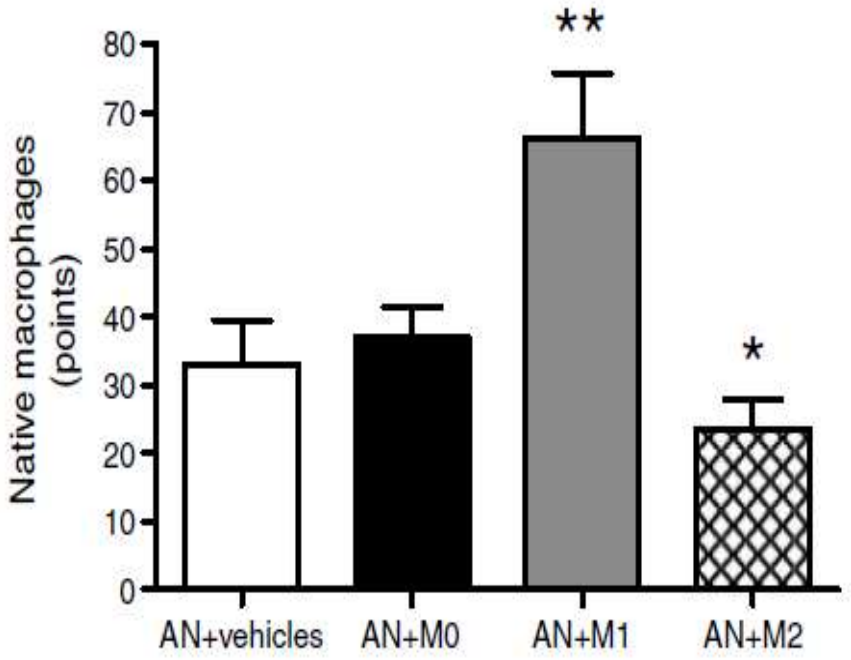

AN + Vehicle
AN + M0
AN + M1
AN + M2
PAS
Trichrome
AN+vehicle
AN+M0
AN+M1
AN+M2
Scores of morphological changes
0
0.5
1
1.5
2
2.5
3
Tubular damage
Interstitial volume
Glomerulosclerosis
Interstitial fibrosis (%)
0
10
20
30
40
50
60
AN+vehicle
AN+M0
AN+M1
AN+M2

TRACKING OF TRANSFUSED MACROPHAGES ??????????????

TRACKING OF TRANSFUSED MACROPHAGES IN VIVO (DAY 28)

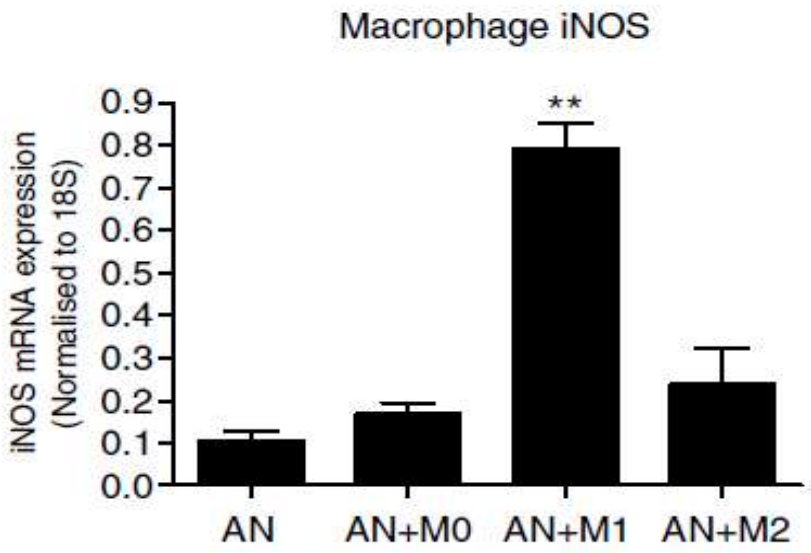


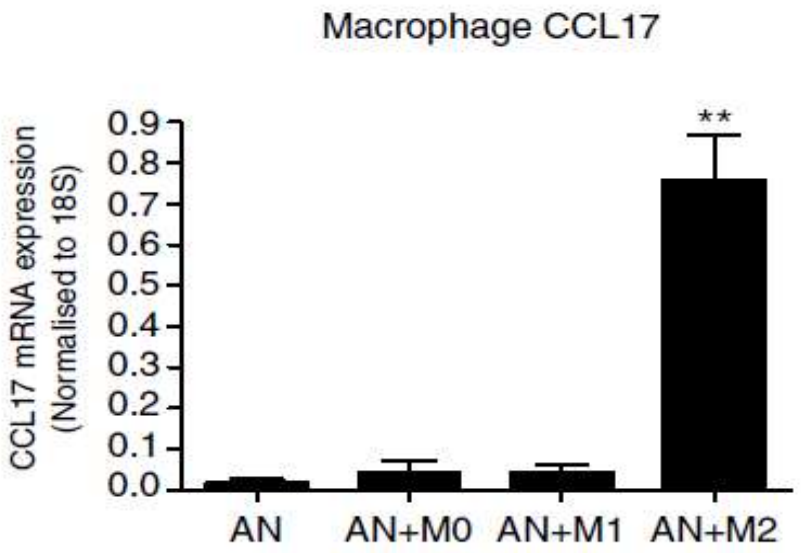


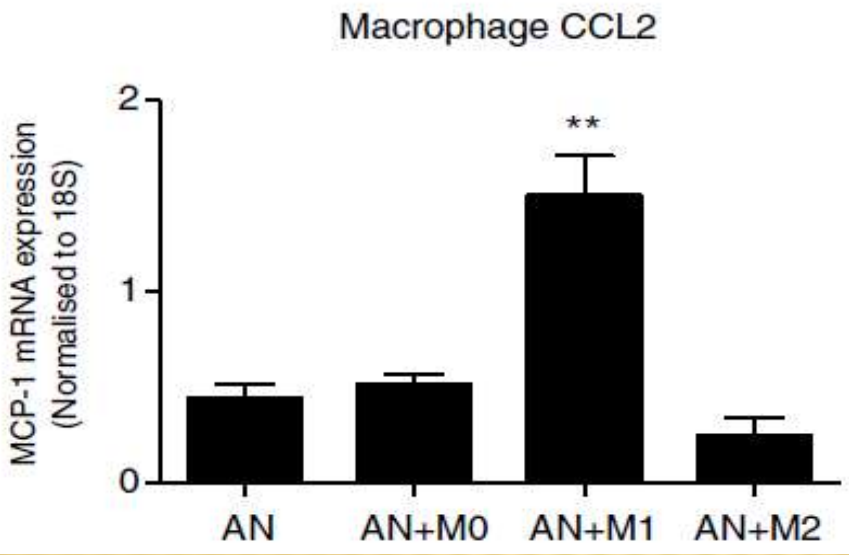


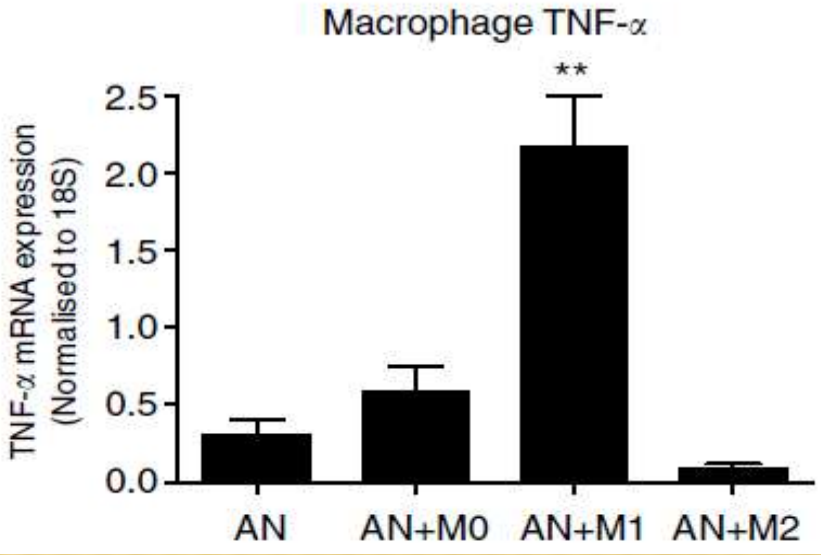
STABILITY OF TRANSFUSED MACROPHAGES ??????????

STABILITY OF TRANSFUSED MACROPHAGES IN VIVO AT DAY 28









2. Regulatory (IL-10/TGF-β stimulated) (M2c) Macrophages In Adriamycin Nephropathy

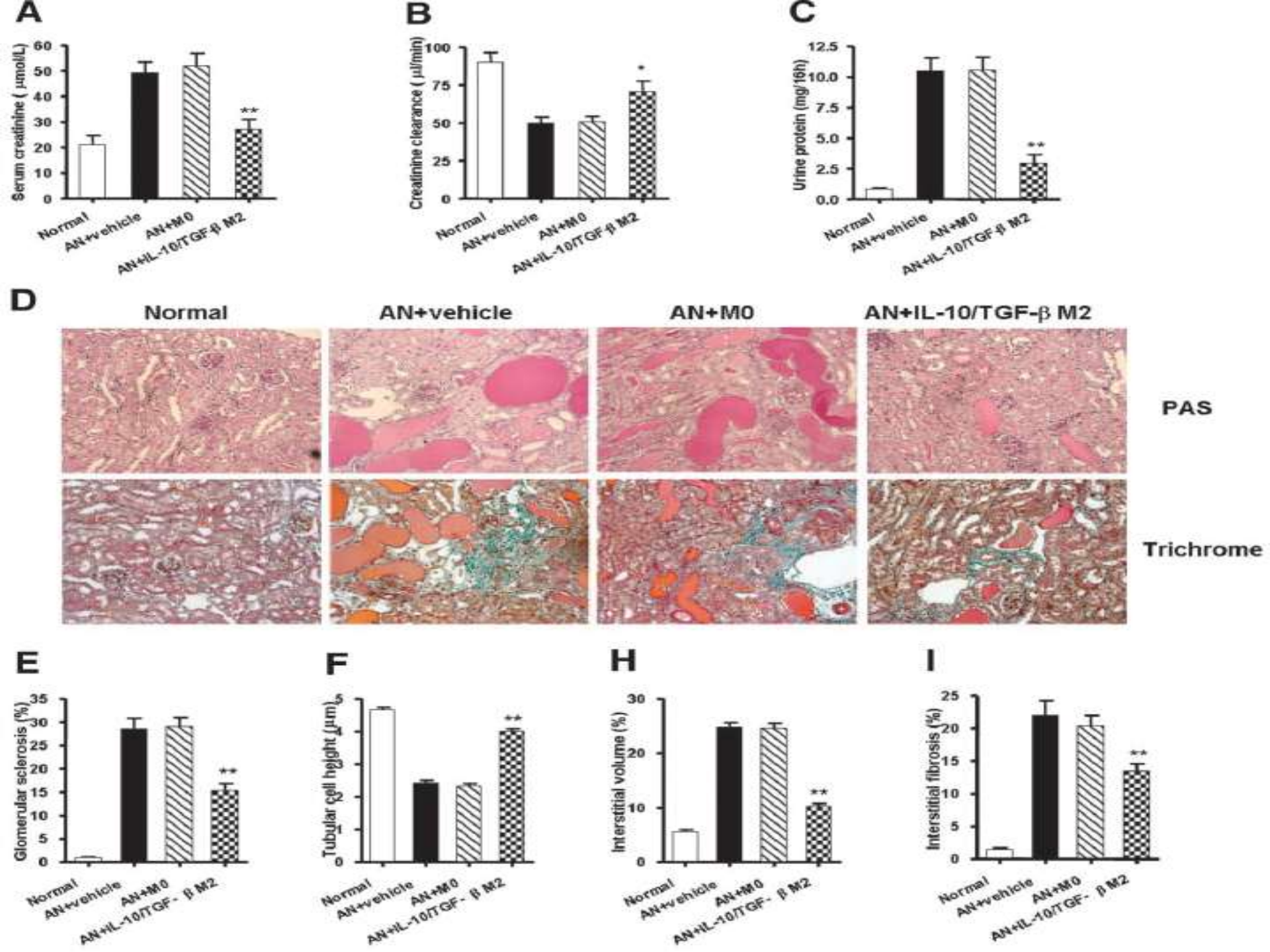
BASIC RESEARCH www.jasn.org

IL-10/TGF-β–Modified Macrophages Induce Regulatory T Cells and Protect against Adriamycin Nephrosis

Qi Cao,* Yiping Wang,* Dong Zheng,* Yan Sun,* Ya Wang,* Vincent W.S. Lee,* Guoping Zheng,* Thian Kui Tan,* Jon Ince,* Stephen I. Alexander,† and David C.H. Harris*

*Centre for Transplantation and Renal Research, University of Sydney, Westmead Millennium Institute, Sydney, New South Wales, Australia; and †Centre for Kidney Research, Children's Hospital at Westmead, Sydney, New South Wales, Australia

J Am Soc Nephrol 21: 933–942, 2010. doi: 10.1681/ASN.2009060592


A
Serum creatinine (μmol/L)
60
50
40
30
20
10
0
**
Normal
AN+vehicle
AN+M0
AN+IL-10/TGF β M2
B
Creatinine clearance (μl/min)
100
75
50
25
0
*
Normal
AN+vehicle
AN+M0
AN+IL-10/TGF β M2
C
Urine protein (mg/16h)
12.5
10.0
7.5
5.0
2.5
0.0
**
Normal
AN+vehicle
AN+M0
AN+IL-10/TGF β M2
D
Normal
AN+vehicle
AN+M0
AN+IL-10/TGF-β M2
PAS
Trichrome
E
Glomerular sclerosis (%)
35
30
25
20
15
10
5
0
**
Normal
AN+vehicle
AN+M0
AN+IL-10/TGF- β M2
F
Tubular cell height (μm)
5
4
3
2
1
0
**
Normal
AN+vehicle
AN+M0
AN+IL-10/TGF- β M2
H
Interstitial volume (%)
30
20
10
0
**
Normal
AN+vehicle
AN+M0
AN+IL-10/TGF- β M2
I
Interstitial fibrosis (%)
25
20
15
10
5
0
**
Normal
AN+vehicle
AN+M0
AN+IL-10/TGF- β M2

REGULATORY EFFECT OF M2c MACROPHAGES

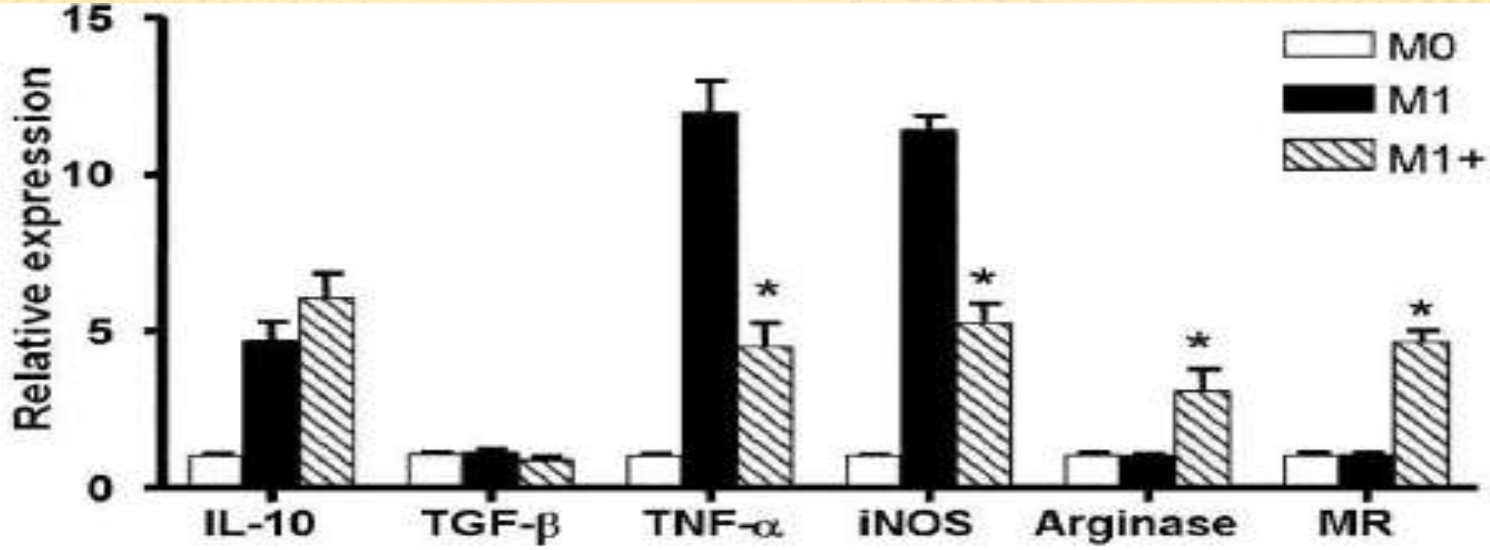
EFFECT OF M2c MACROPHAGES ON ENDOGENOUS INFLAMMATORY CELLS

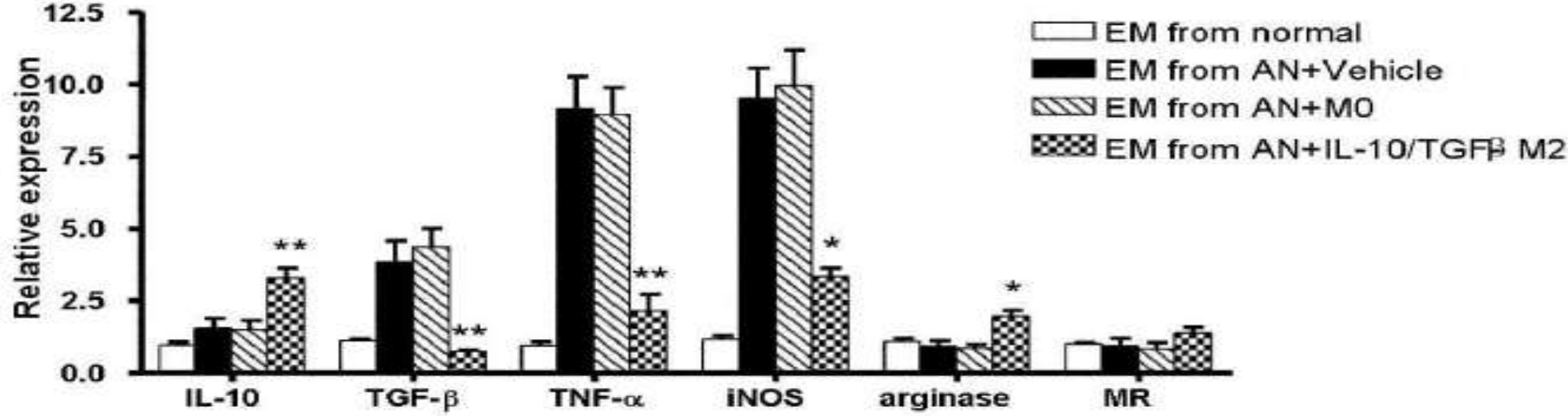
Parameter	AN+Vehicle	AN+M0	AN+IL-10/ TGF-β M2
$CD4^+$ T cells	72.3 ± 13.6	70.3 ± 15.7	25.3 ± 7.2[a]
$CD8^+$ T cells	36.3 ± 5.5	38.1 ± 4.7	17.6 ± 5.6[a]
Macrophages	64.3 ± 10.8	66.4 ± 10.1	42.9 ± 8.4[a]

Data are means ± SEM of cells per ×400 field.

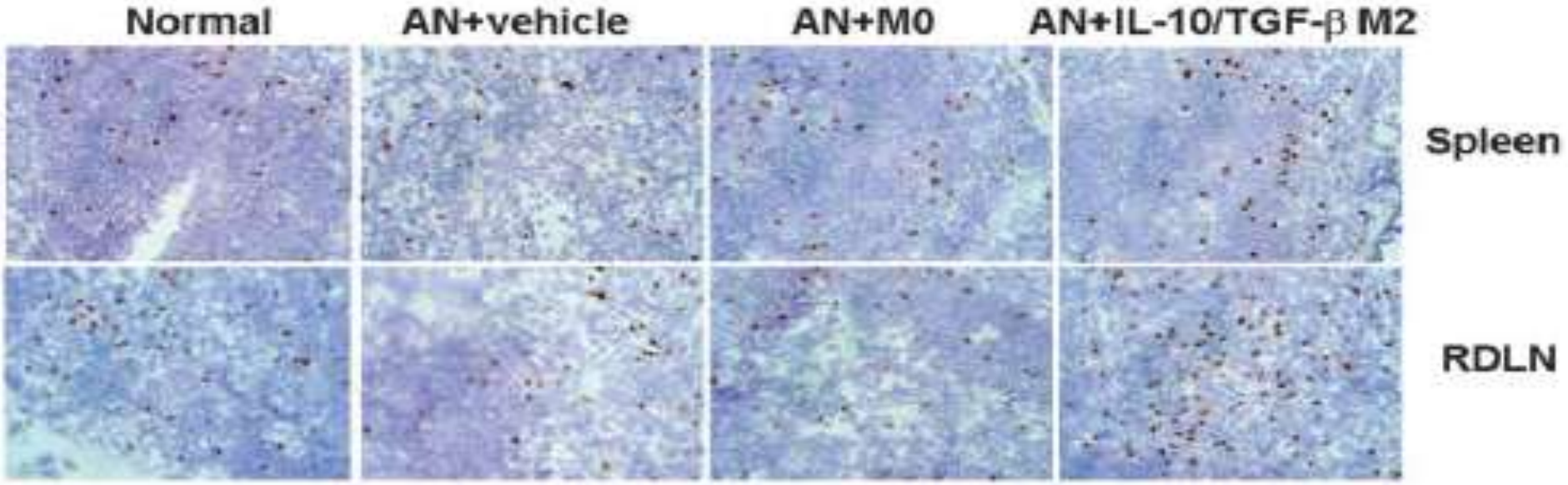
[a] $P < 0.01$ *versus* AN+M0.

M2c SUPPRESSES M1 *IN VITRO AND ENDOGENOUS RENAL* MACROPHAGES *IN VIVO*



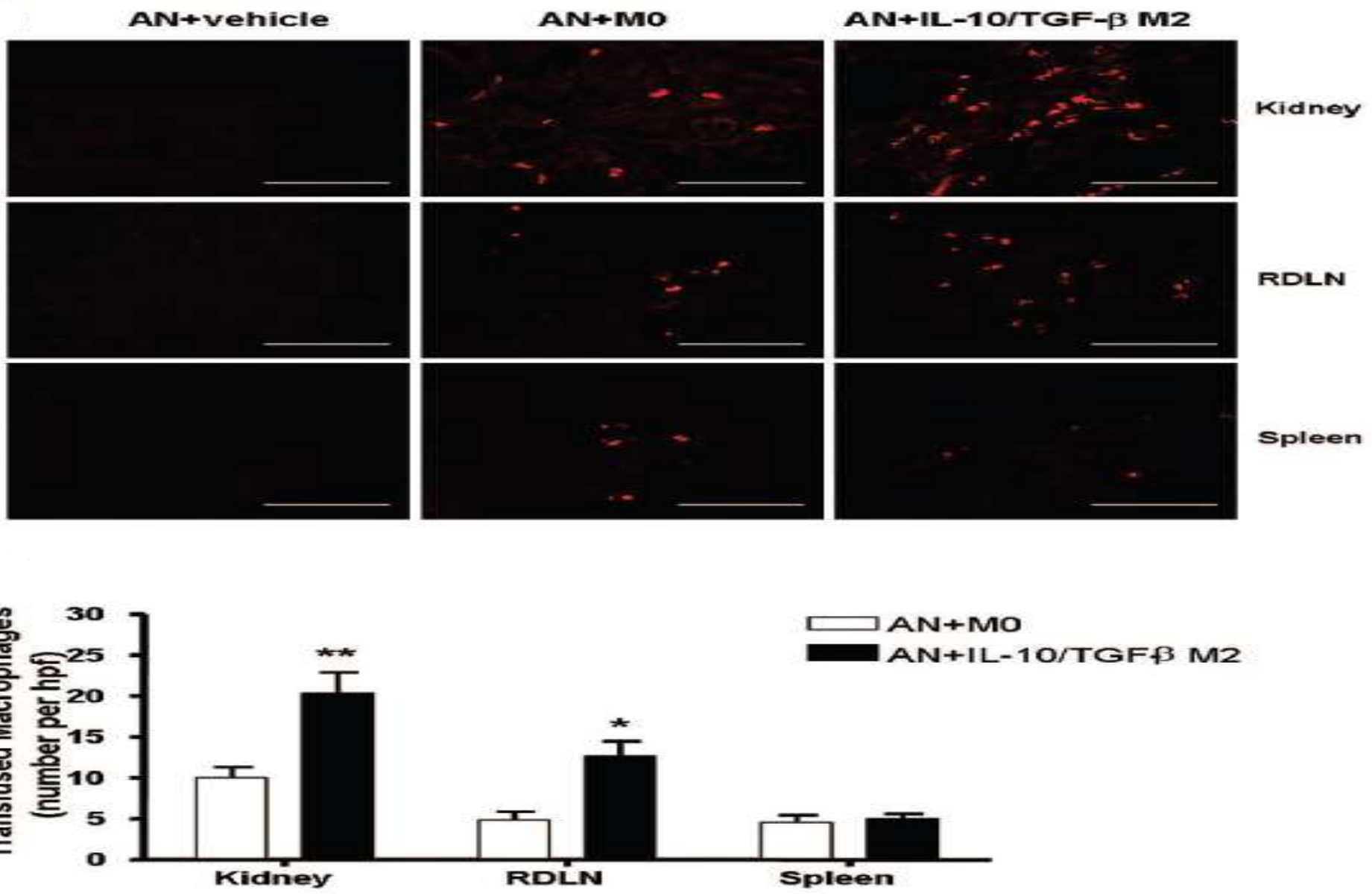


M2c MACROPHAGES INDUCES Tregs IN VITRO & IN VIVO



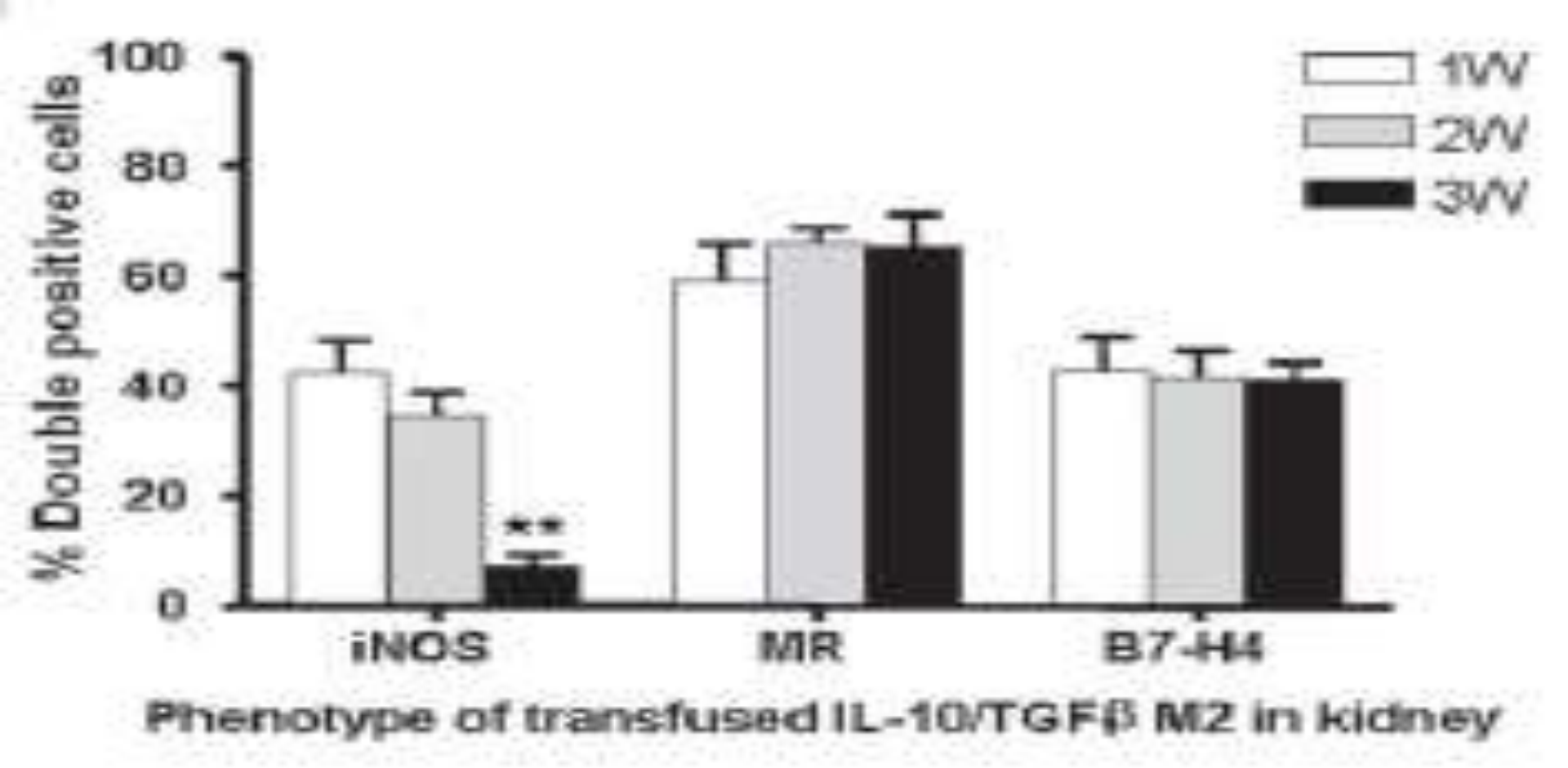
TRACKING OF TRANSFUSED MACROPHAGES ??????????????

SELECTIVE TRACKING OF TRANSFUSED M2c (28 days)



STABILITY OF TRANSFUSED MACROPHAGES ??????????

MAINTENANCE OF ANTI-INFLAMMATORY PHENOTYES *IN VIVO OF TRANSFUSED M2c*



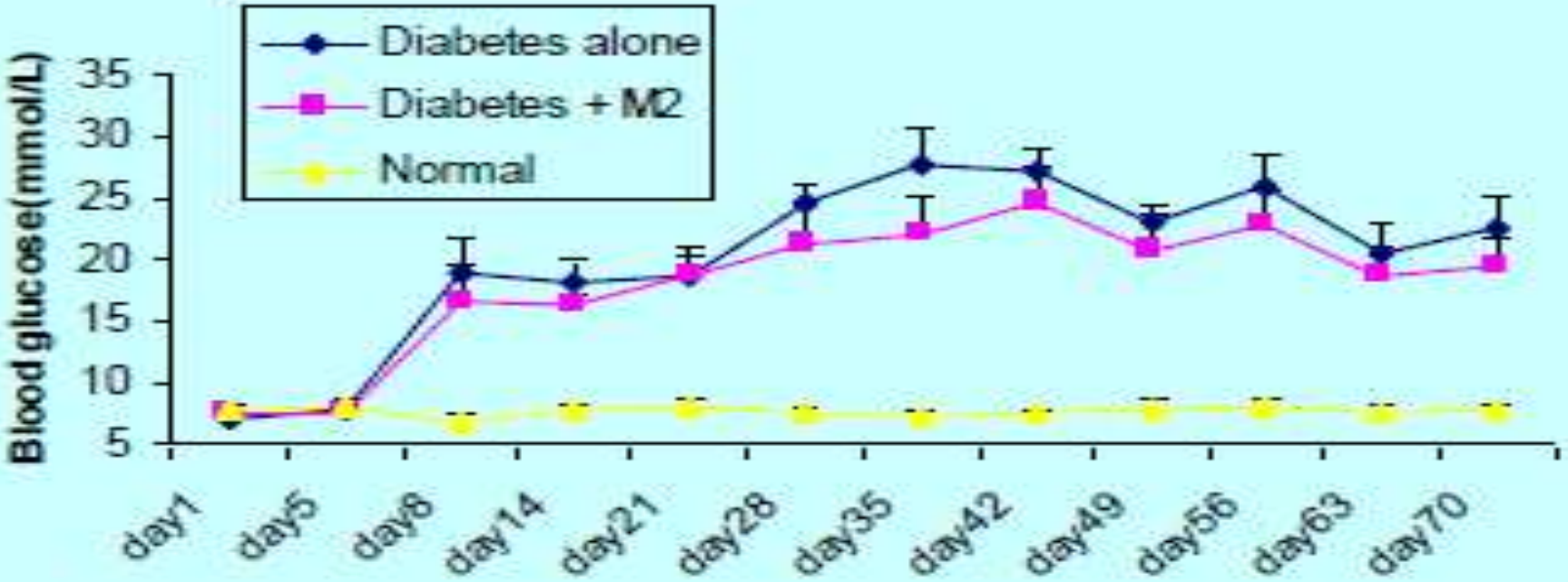
3. Wound-healing (M2a) Macrophages in Diabetic Nephropathy

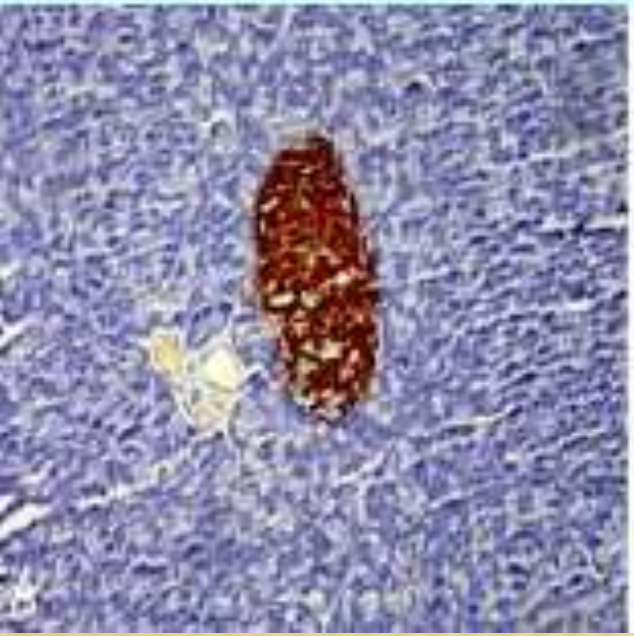
Regulatory macrophages protect against renal injury in murine streptozotocin-induced diabetes

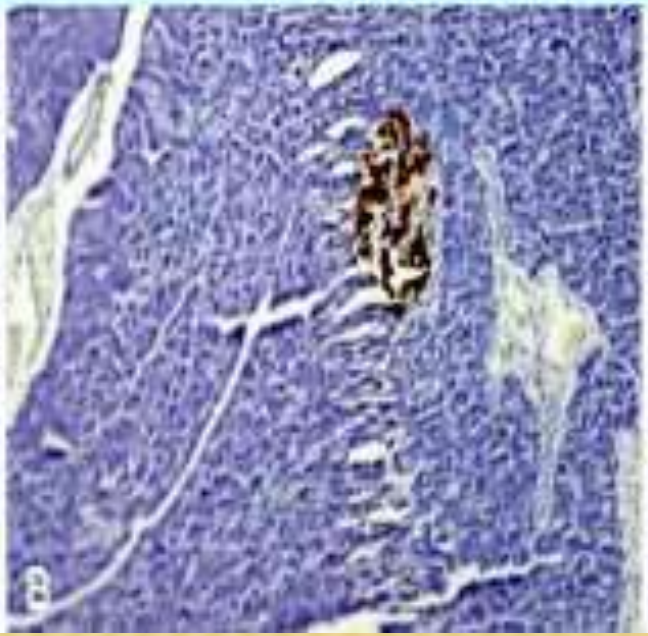
D Zheng, YP Wang, VWS Lee, Q Cao, G Zheng, Y Sun, Y Wang, SI Alexander[1] and DCH Harris

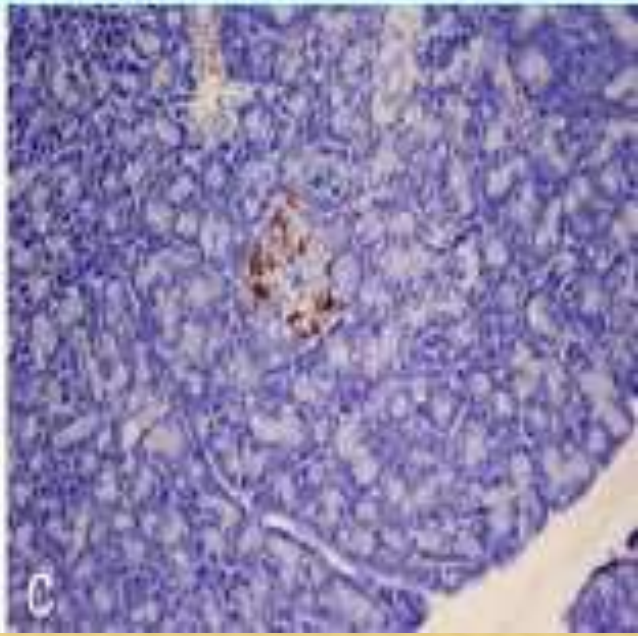
Centre for Transplant and Renal Research, The University of Sydney, Westmead Millennium Institute, Sydney, NSW, Australia and [1]Centre for Kidney Research, Children's Hospital at Westmead, Sydney, NSW, Australia.

Macrophages were separated from splenocytes of BALB/c mice and cultured with IL-4 and IL-13. Mice underwent adoptive transfer with $1x10^6$ M2/per mouse, followed by tail injection with two doses of STZ (75mg/kg and150mg/kg). Blood glucose levels were monitored daily. Mice were sacrificed at the 10^{th} week after STZ injection. Renal function and histopathological injury were assessed.



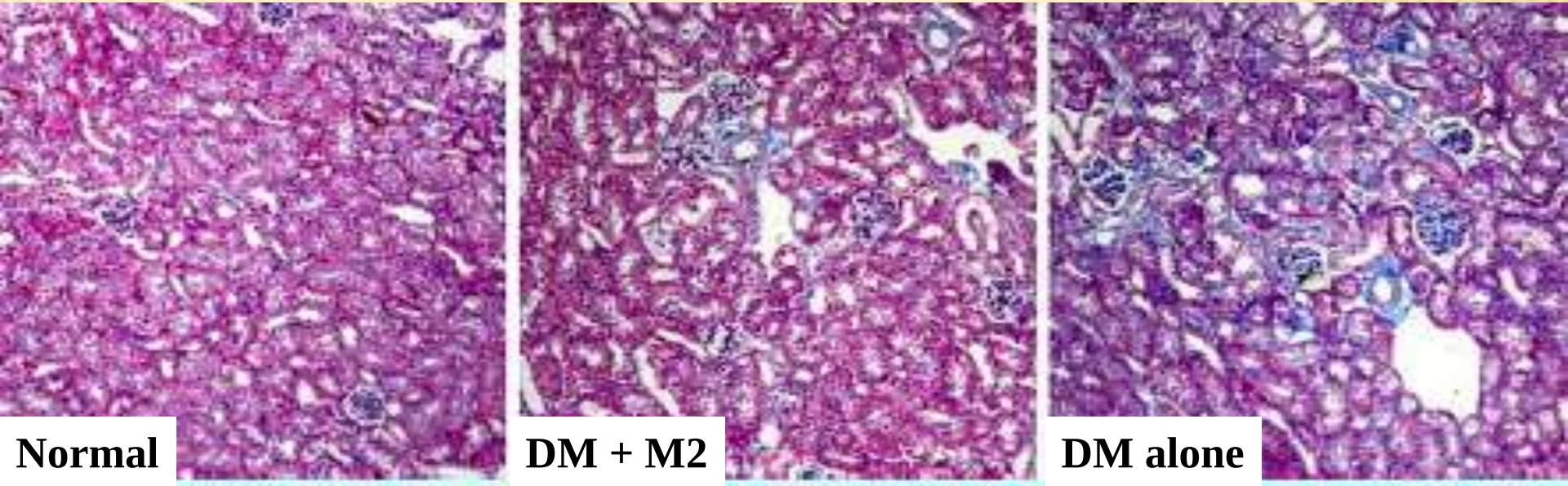


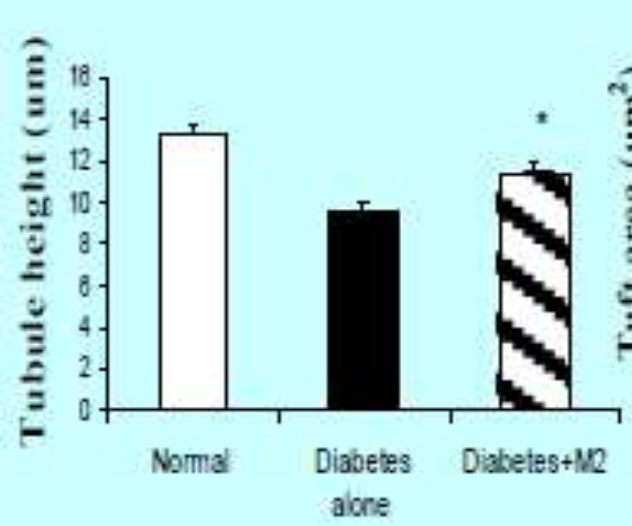


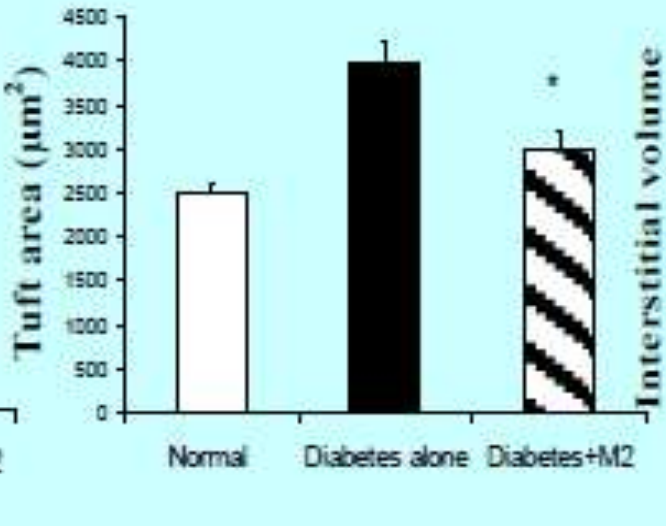


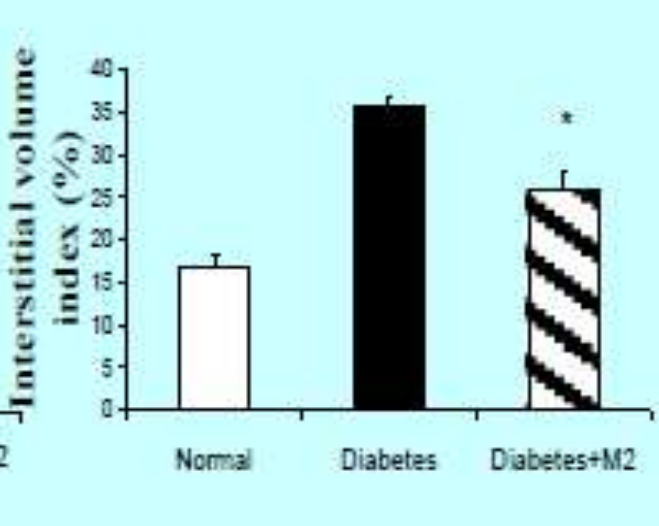
Normal **DM + M2** **DM alone**

M2a MACROPHAGES AMELIORATES RENAL FIBROSIS.

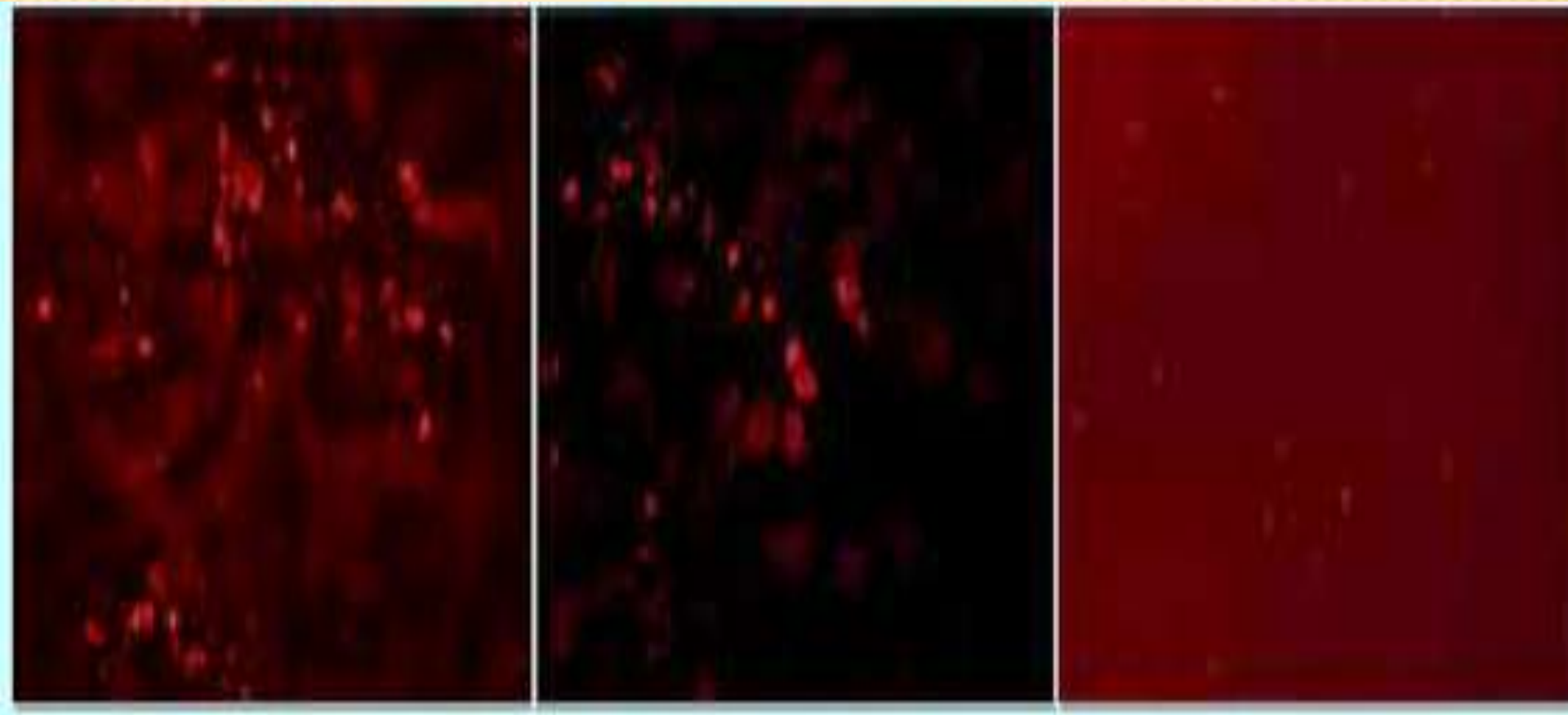








IN VIVO TRACKING OF TRANSFERRED MACROPHAGES 10 WEEKS



Kidney Pancreas Spleen

CAN M2a AMELIORATE RENAL INJURY IN ESTABLISHED DIABETIC NEPHROPATHY ??????????????

M2a

VS

M2c

BMD
VS
SPLENIC MACROPHAGES

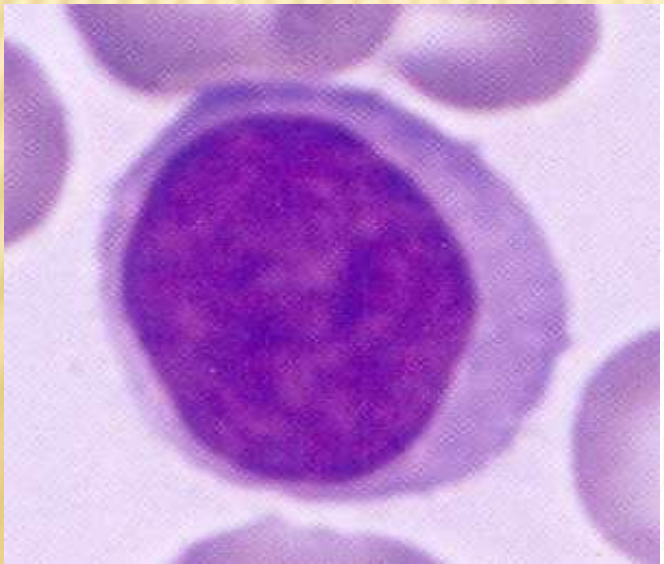
OBSTACLES FOR USE IN HUMAN

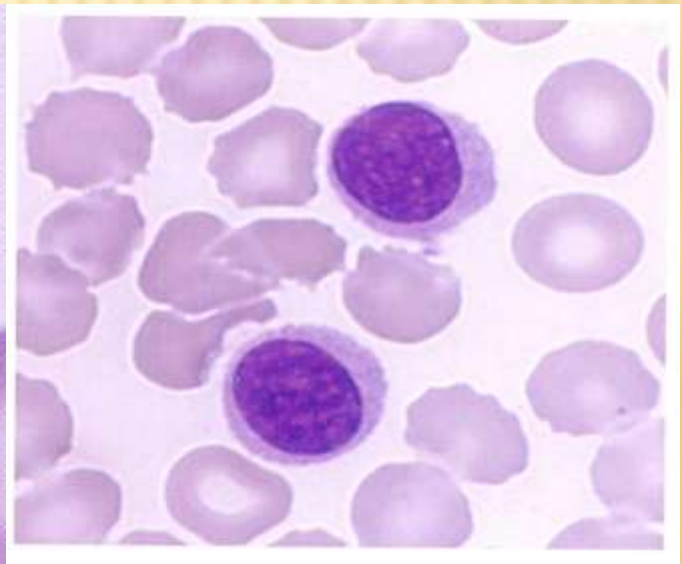
- Adequate purity and sufficient numbers of macrophages from humans for adoptive transfer.
- Dose, timing and frequency of use of regulatory cells.
- Immunosupression: malignancy & infection.
- Stability and possibility of phenotypic switch.
- Lack of human studies.
- The effect of M2 macrophages in advanced disease is unproven.

LYMPHOCYTES

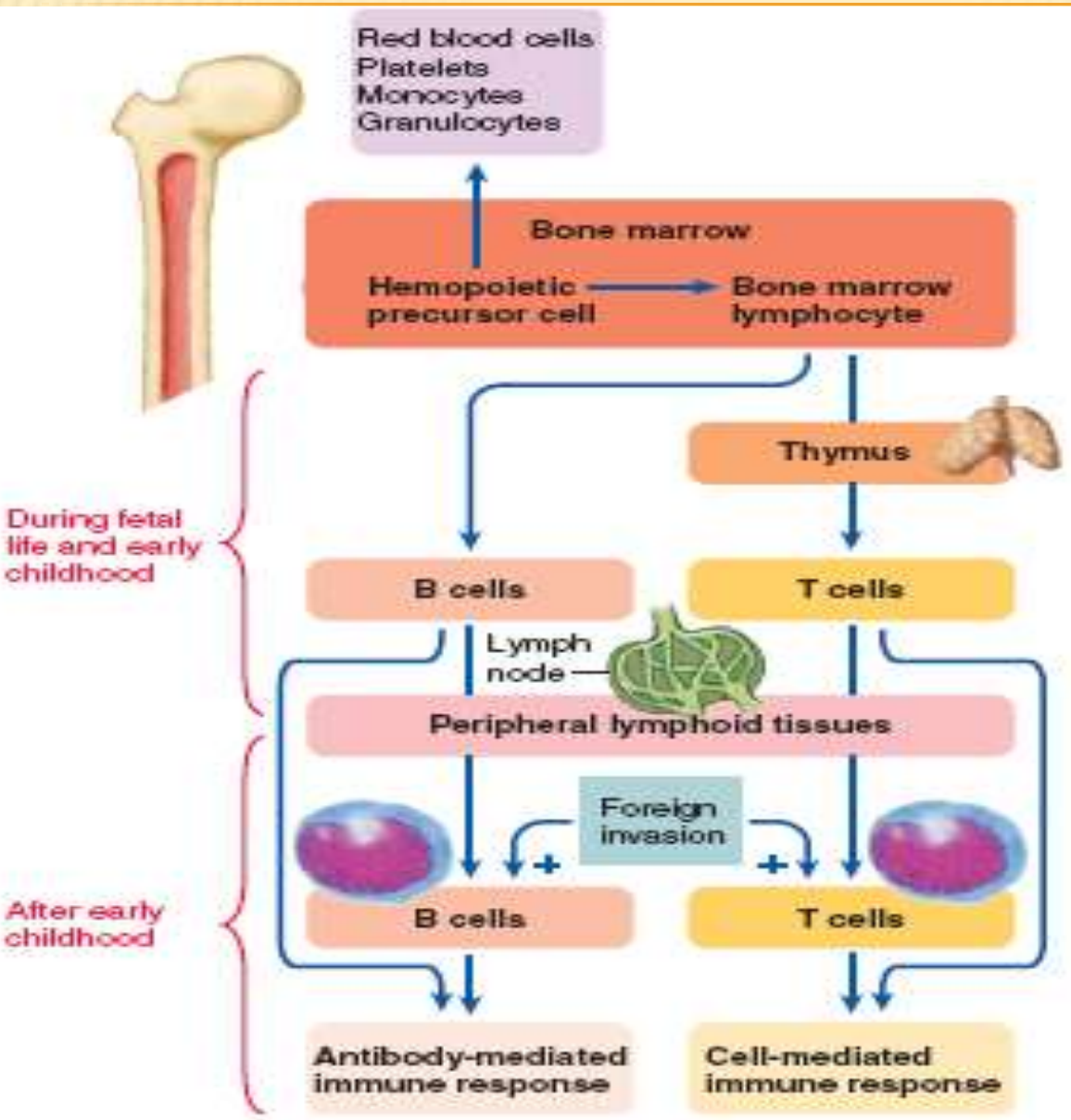
- T lymphocytes: cause direct destruction of virus invaded cells and mutant cells (Cell mediated immunity)

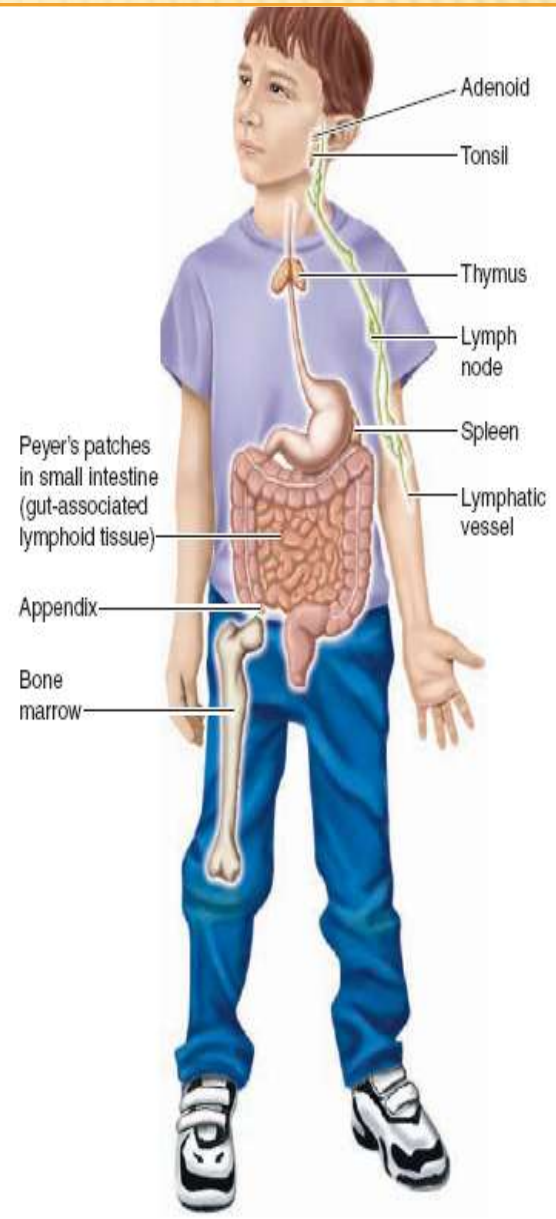
- B lymphocytes: secrete antibodies that indirectly lead to the destruction of foreign material (Humoral immunity)

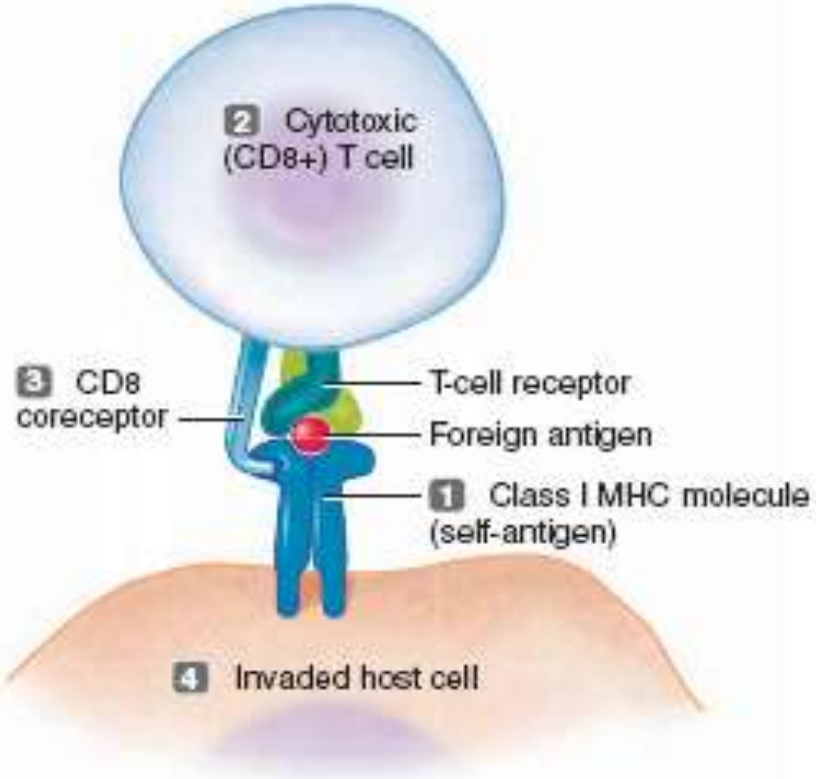




ORIGIN OF T AND B LYMPHOCYTES







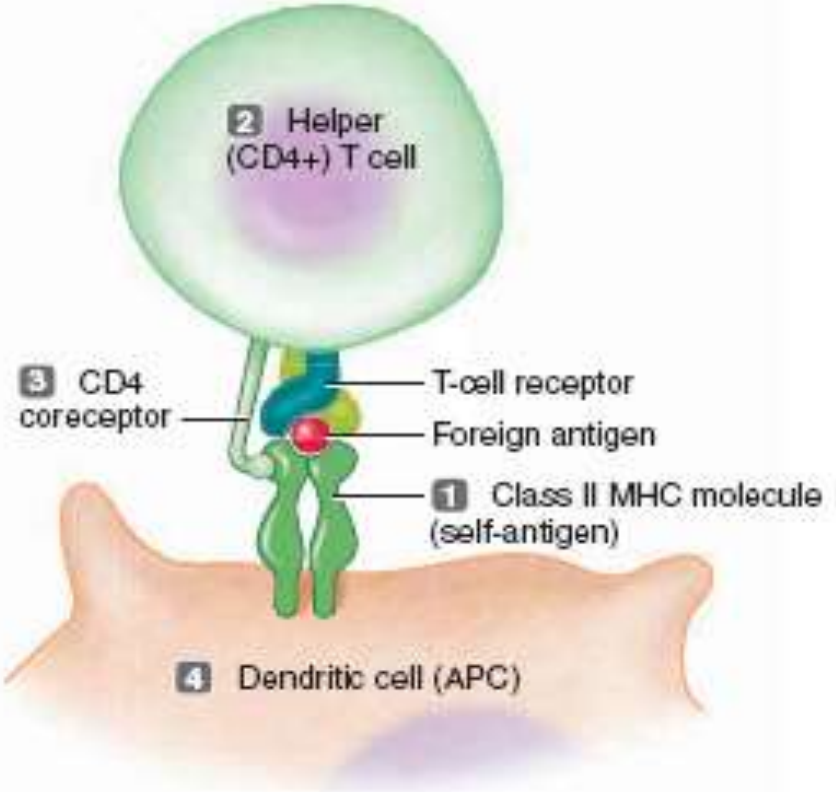
1 Class I MHC molecules are found on surface of all cells.

2 They are recognized only by cytotoxic (CD8+) T cells.

3 CD8 coreceptor links the two cells together.

4 Linked in this way, cytotoxic T cells can destroy body cells if invaded by foreign (viral) antigen.

(a) Class I MHC self-antigens



1 Class II MHC molecules are found on the surface of immune cells with which helper T cells interact: dendritic cells, macrophages, and B cells.

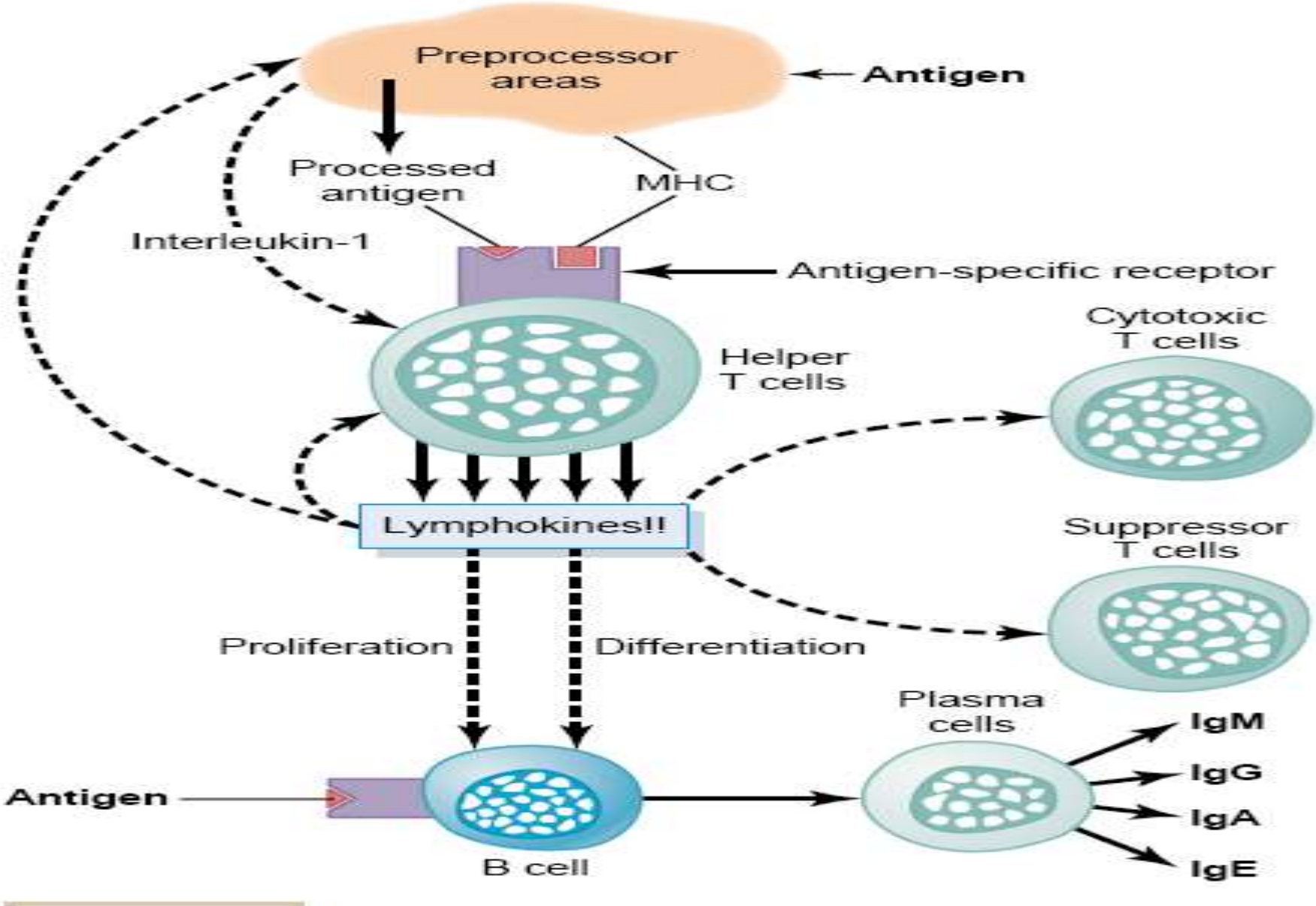
2 They are recognized only by helper (CD4+) T cells.

3 CD4 coreceptor links the two cells together.

4 To be activated, helper T cells must bind with a class II MHC-bearing APC (dendritic cell or macrophage). To activate B cells, helper T cell must bind with a class II MHC-bearing B cell with displayed foreign antigen.

(b) Class II MHC self-antigens

PIVOTAL ROLE OF HELPER T CELL



ROLE OF LYMPHOCYTES IN ISCHEMIC AKI (IRI)

- T cells were not expected to participate in the initial renal injury based on traditional ideas about the immunological functions of T cells.

LYMPHOCYTES ROLE IN EARLY & LATE RENAL INJUIRY

The Role of the B7 Costimulatory Pathway in Experimental Cold Ischemia/Reperfusion Injury

Moriatsu Takada,* Anil Chandraker,‡ Kari C. Nadeau,§ Mohamed H. Sayegh,‡ and Nicholas L. Tilney*

**Surgical Research Laboratory and Department of Surgery, and ‡Renal Division, Department of Medicine, Brigham and Women's Hospital; and §Department of Pediatrics, Children's Hospital Medical Center, Harvard Medical School, Boston, Massachusetts 02115*

M.H. Sayegh and N.L. Tilney are co-senior authors.
Address correspondence to Dr. Mohamed H. Sayegh, Brigham and Women's Hospital, 75 Francis St., Boston, MA 02115. Phone: 617-732-5259; FAX: 617-732-5254; E-mail: sayegh@bustoff.bwh.harvard.edu
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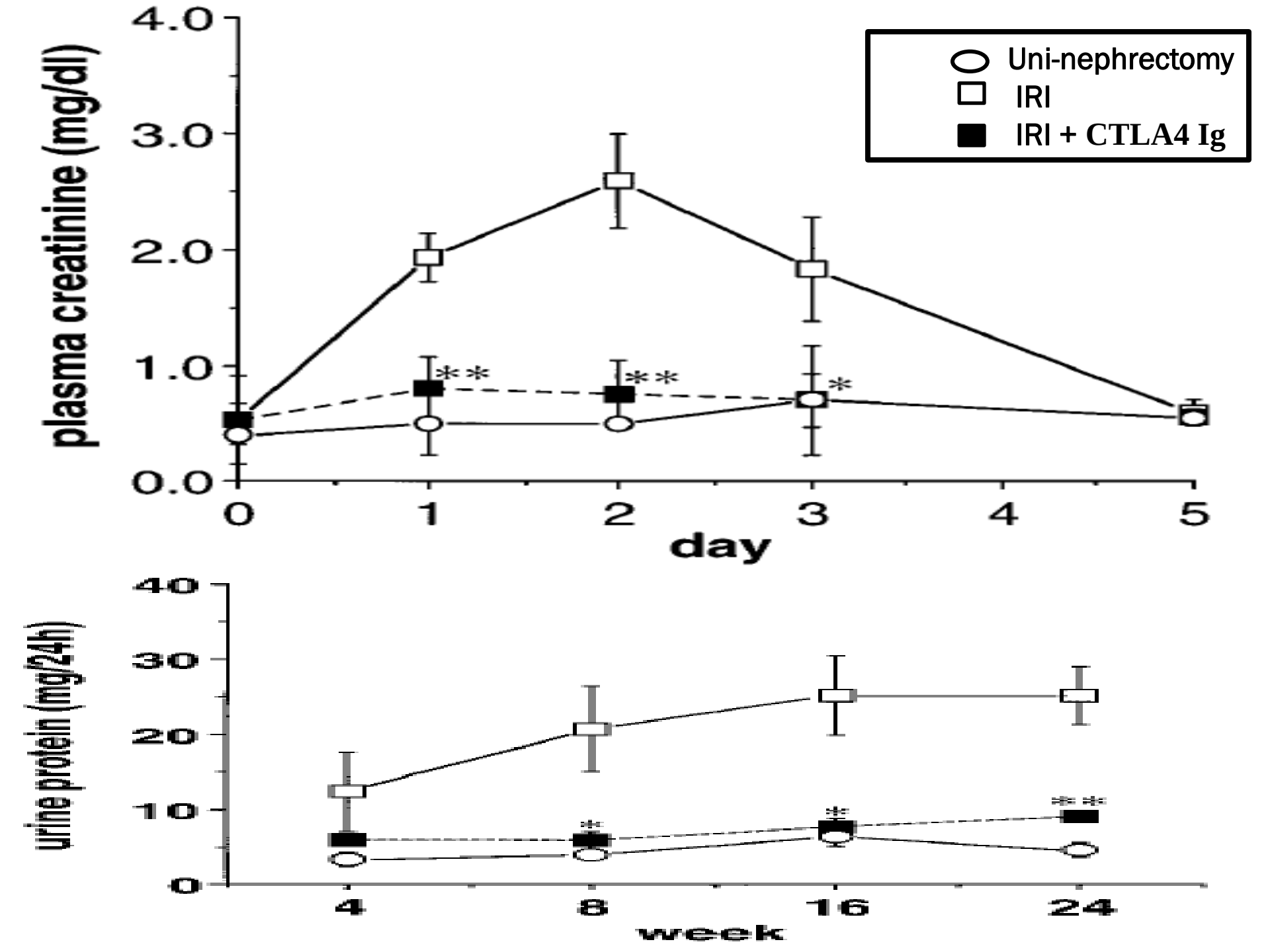
Volume 100, Number 5, September 1997, 1199–1203
http://www.jci.org

Blockade of T cell CD28-B7 costimulation with CTLA4Ig Ig both on the day of renal IRI and during the first week after IRI in uninephrectomatized rats


Uni-nephrectomy
IRI
IRI + CTLA4 Ig
plasma creatinine (mg/dl)
4.0
3.0
2.0
1.0
0.0
0
1
2
3
4
5
day
**
**
*
urine protein (mg/24h)
40
30
20
10
0
4
8
16
24
week
*
*
**

T OR B LYMPHOCYTES IN RENAL INJUIRY ??????????????

eBioscience
An Affymetrix Company
Tandems still bright after a 3-day fix?
Learn More

THE JOURNAL OF IMMUNOLOGY

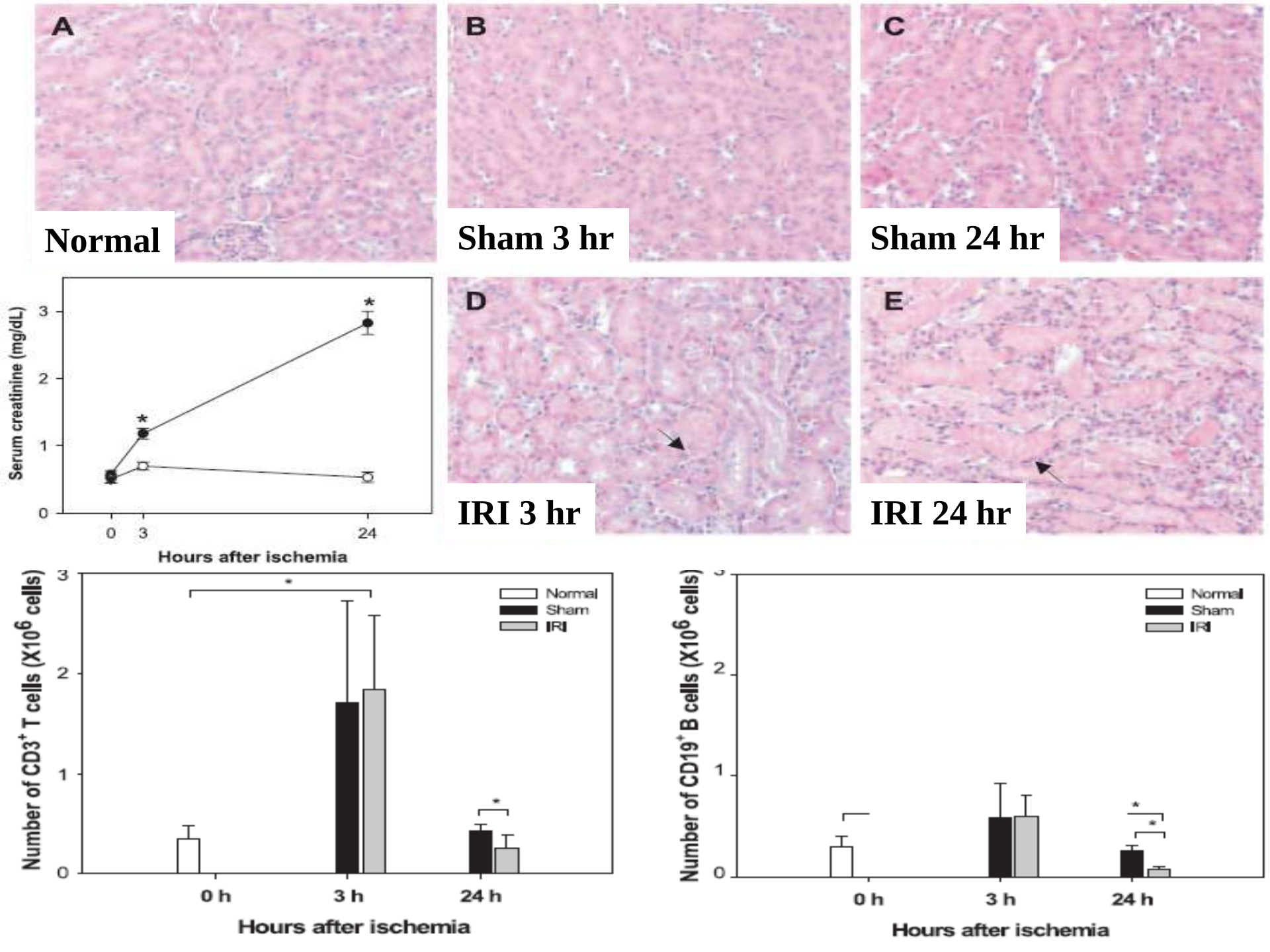
Phenotypic and Functional Characterization of Kidney-Infiltrating Lymphocytes in Renal Ischemia Reperfusion Injury

This information is current as of November 25, 2012.

Dolores B. Ascon, Sergio Lopez-Briones, Manchang Liu, Miguel Ascon, Vladimir Savransky, Robert B. Colvin, Mark J. Soloski and Hamid Rabb

J Immunol 2006; 177:3380-3387; ;
http://www.jimmunol.org/content/177/5/3380

Male C57BL/6J wild-type were bluntly dissected and a microvascular clamp was placed on each renal pedicle for 30 min and compared with Sham operated animals.


A
Normal
B
Sham 3 hr
C
Sham 24 hr
Serum creatinine (mg/dL)
Hours after ischemia
D
IRI 3 hr
E
IRI 24 hr
Number of CD3+ T cells (X10^6 cells)
Normal
Sham
IRI
0 h
3 h
24 h
Hours after ischemia
Number of CD19+ B cells (X10^6 cells)
Normal
Sham
IRI
0 h
3 h
24 h
Hours after ischemia

CD4 OR CD8 T LYMPHOCYTES ??????????

Identification of the CD4+ T cell as a major pathogenic factor in ischemic acute renal failure

Melissa J. Burne,[1] Frank Daniels,[1] Asmaa El Ghandour,[1] Shamila Mauiyyedi,[2] Robert B. Colvin,[2] Michael P. O'Donnell,[1] and Hamid Rabb[1]

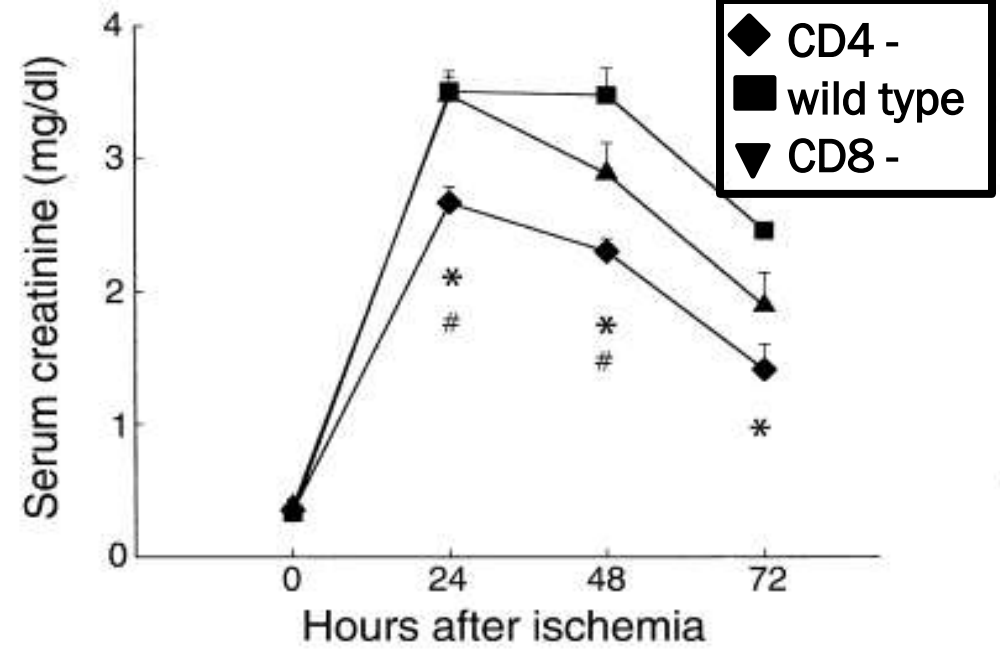
[1]Division of Nephrology, Hennepin County Medical Center, University of Minnesota, Minneapolis, Minnesota, USA
[2]Department of Pathology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA

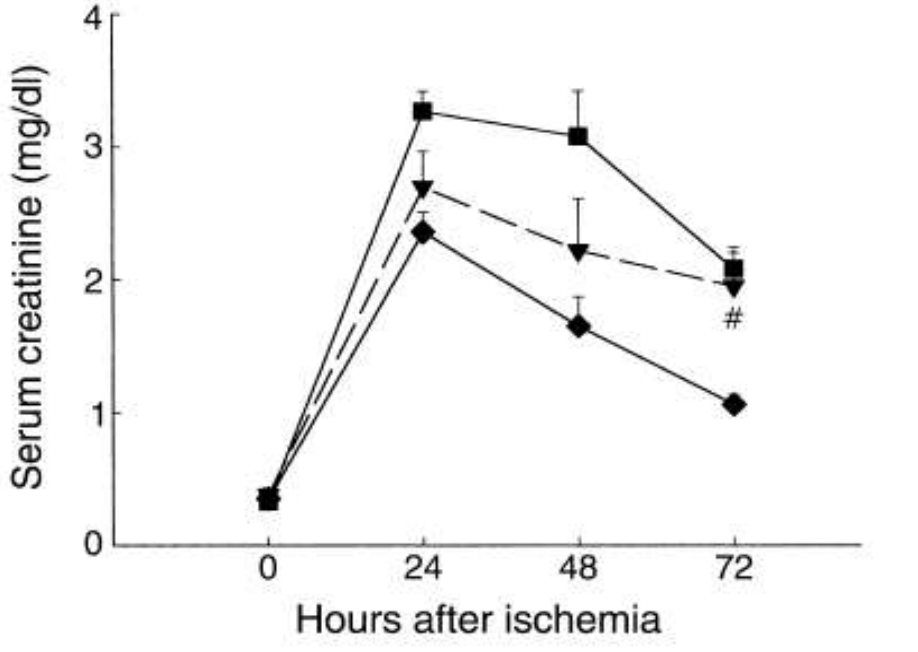
Address correspondence to: Hamid Rabb, Johns Hopkins School of Medicine, Ross Building, Room 970, 720 Rutland Avenue, Baltimore, Maryland 21205, USA. Phone: (410) 502-1555; Fax: (410) 614-5129; E-mail: hrabbl@jhmi.edu.

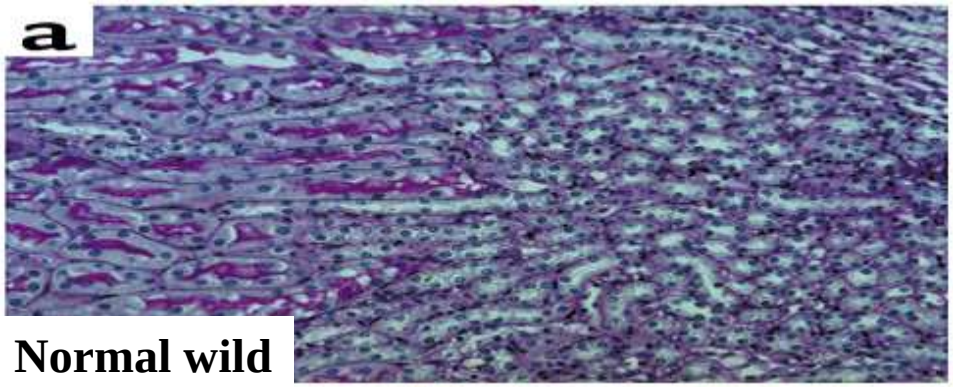
Received for publication December 27, 2000, and accepted in revised form September 17, 2001.

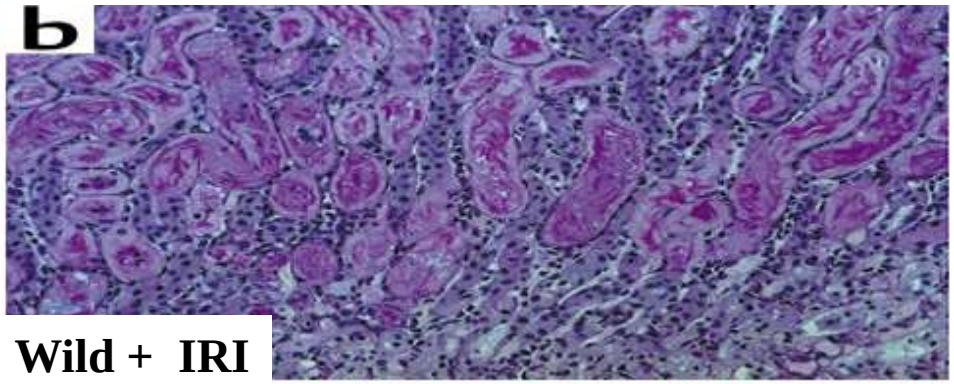
The Journal of Clinical Investigation | November 2001 | Volume 108 | Number 9

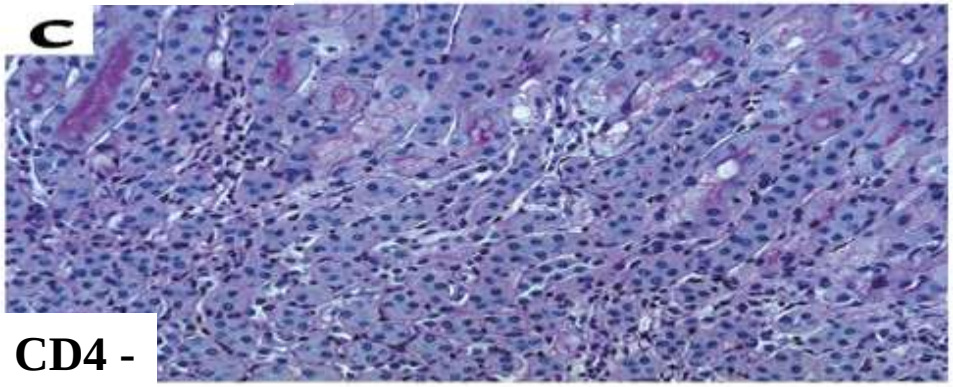
They compared IRI in C57BL/6 wild-type, *nu/nu mice & nu/nu mice were adoptively transferred with wild-type T cells.*

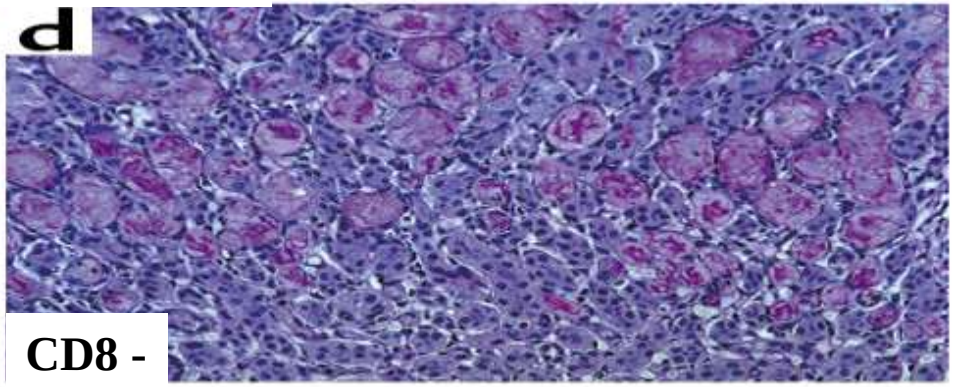

CD4 -
wild type
CD8 -
Serum creatinine (mg/dl)
0
1
2
3
4
0
24
48
72
Hours after ischemia
*
#
*
#
*


Serum creatinine (mg/dl)
0
1
2
3
4
0
24
48
72
Hours after ischemia
#


a
Normal wild


b
Wild + IRI


c
CD4 -


d
CD8 -

- CD4 T-cell has 2 subsets:
  - Th1 phenotype: pathogenic
  - Th2 phenotype: protective

DOES LYMPHOCYTES HAVE ANY ROLE IN RENAL REPAIR ????????

BASIC RESEARCH www.jasn.org

Regulatory T Cells Suppress Innate Immunity in Kidney Ischemia-Reperfusion Injury

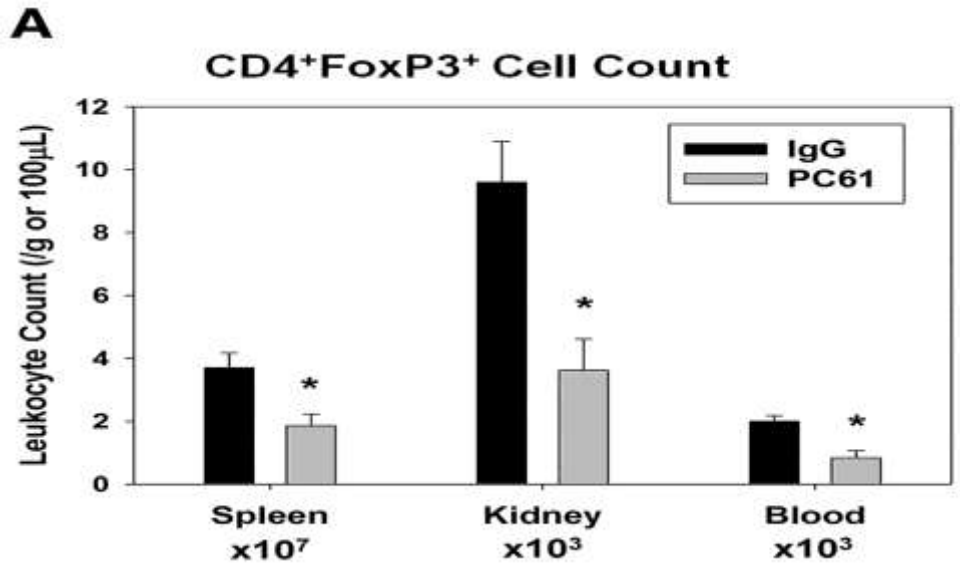
Gilbert R. Kinsey, Rahul Sharma, Liping Huang, Li Li, Amy L. Vergis, Hong Ye, Shyr-Te Ju, and Mark D. Okusa

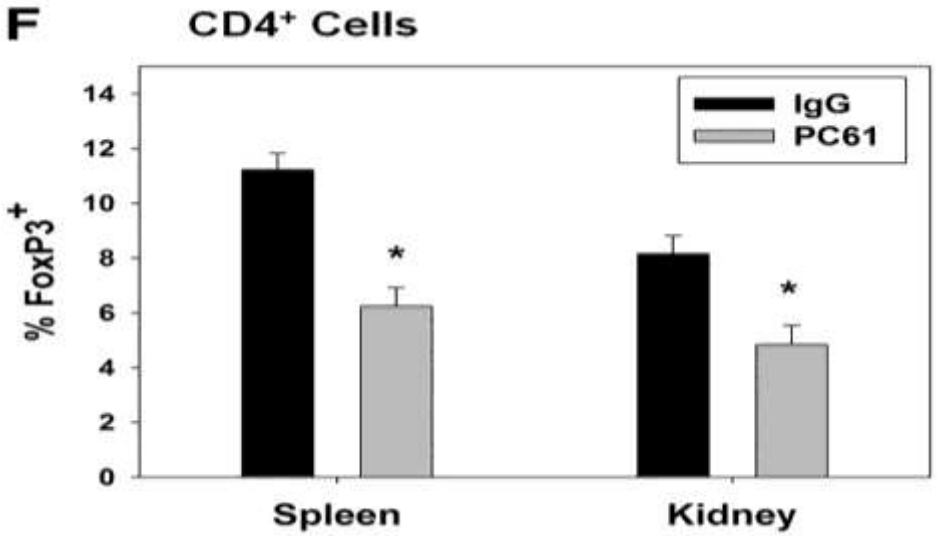
Division of Nephrology and Center for Immunity, Inflammation and Regenerative Medicine, University of Virginia Health System, Charlottesville, Virginia

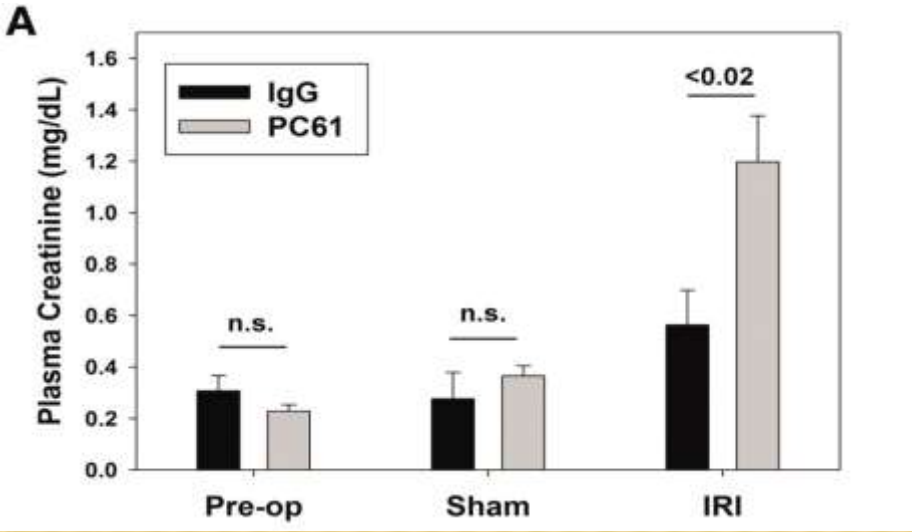
J Am Soc Nephrol 20: 1744–1753, 2009. doi: 10.1681/ASN.2008111160

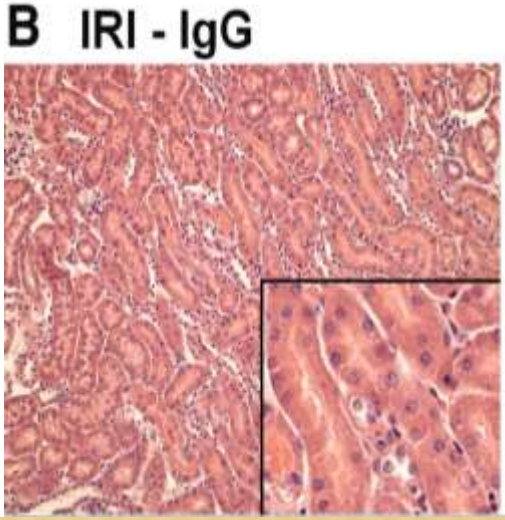
Partial depletion of Tregs with an anti-CD25 mAb before IRI. Adoptive transfer of lymph node cells from wild-type mice or FoxP3-deficient Scurfy mice into T cell– and B cell– deficient RAG-1 knockout mice to generate mice with and without FoxP3 Tregs, respectively.

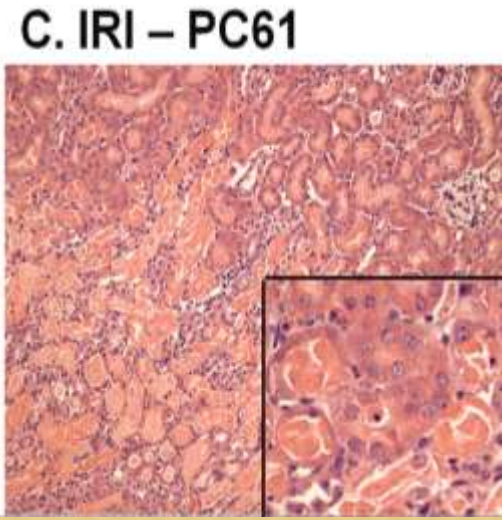
CD25 MAB (PC61) ADMINISTRATION REDUCES Tregs & POTENTIATES IRI





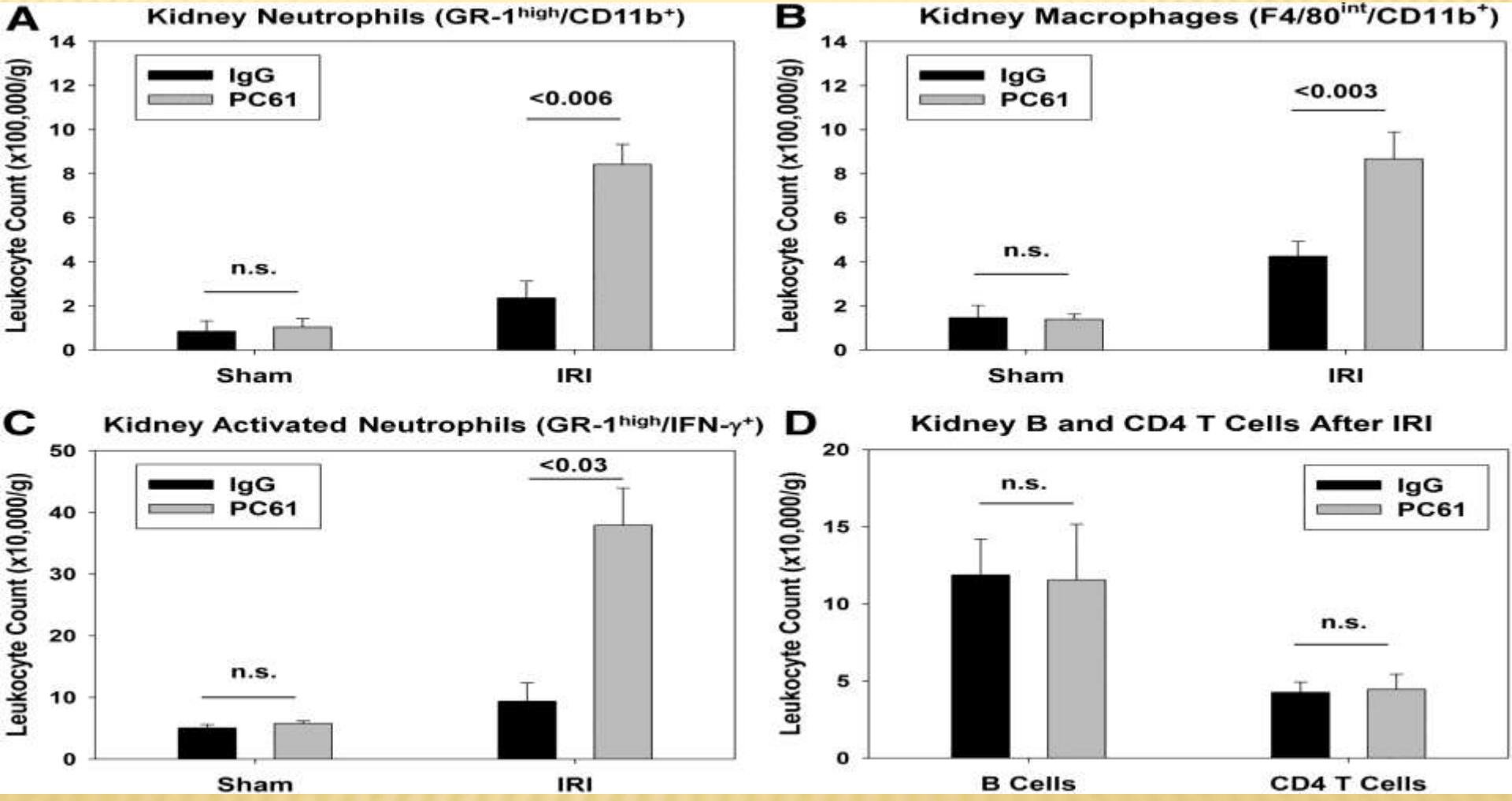






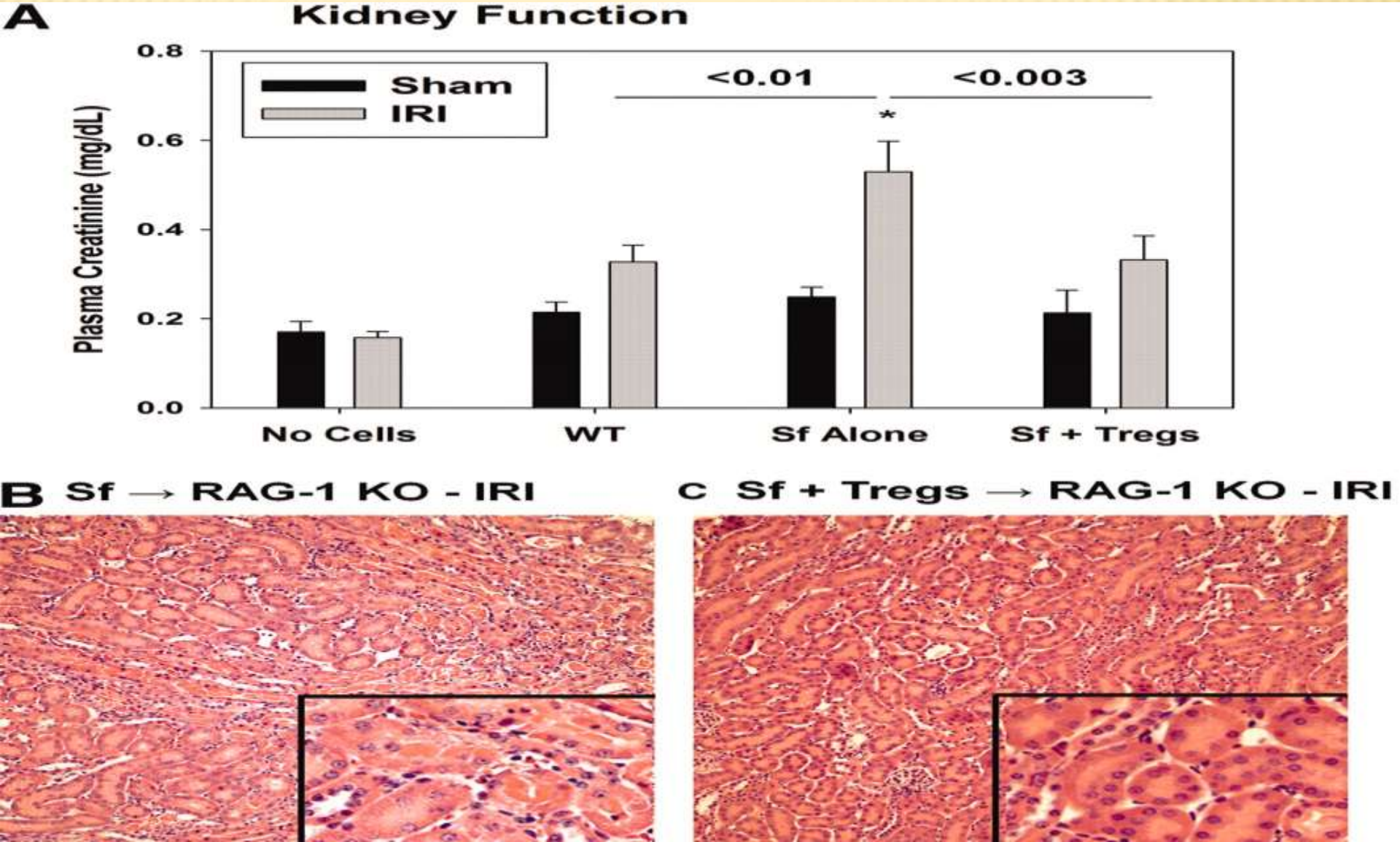
Kinsey G R et al. JASN 2009;20:1744-1753

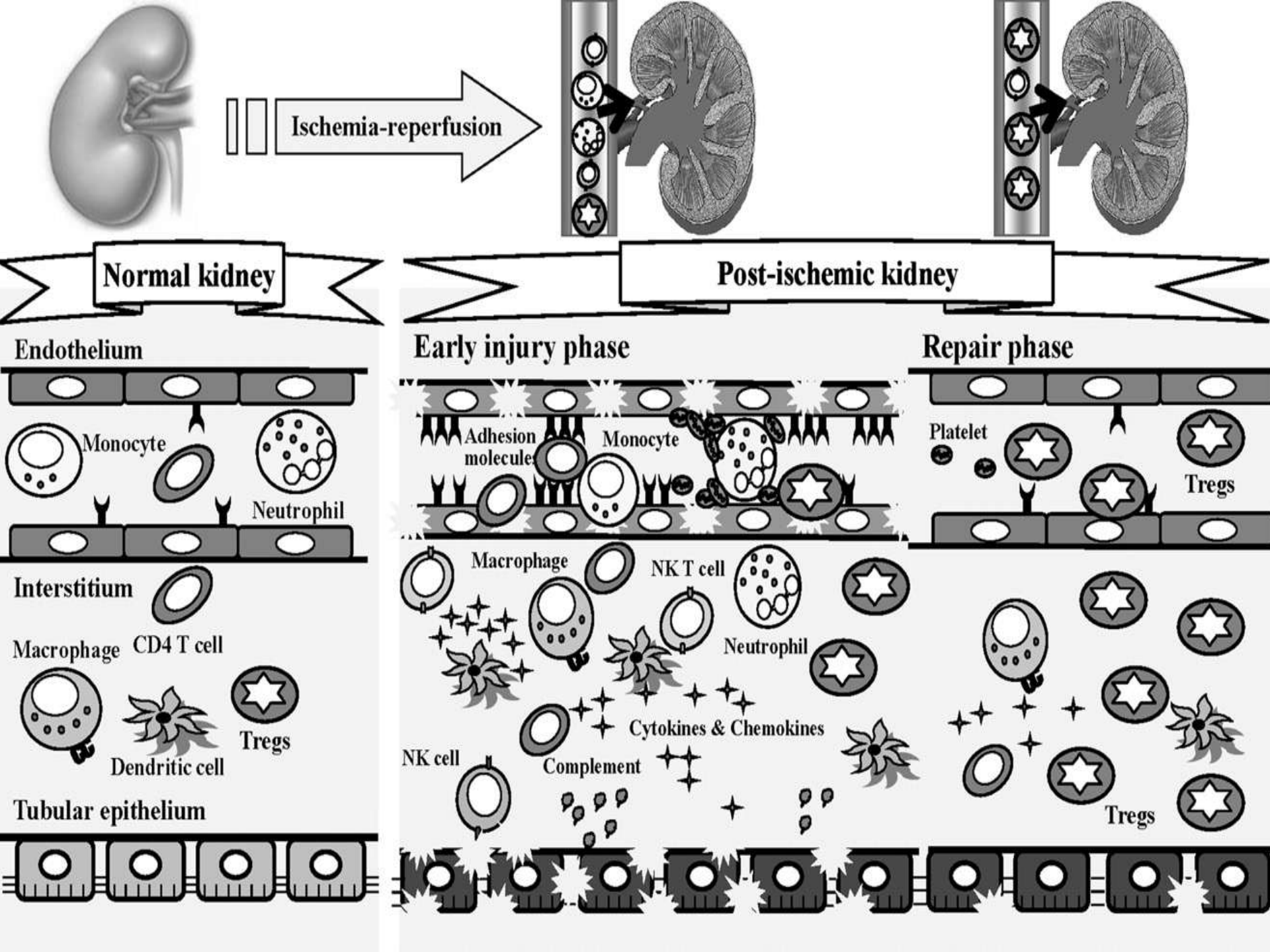
PARTIAL Treg DEPLETION ENHANCES LEUKOCYTE ACCUMULATION AFTER IR.



Kinsey G R et al. JASN 2009;20:1744-1753

Treg REPLETION INHIBITS KIDNEY IRI




Ischemia-reperfusion
Normal kidney
Post-ischemic kidney
Endothelium
Monocyte
Neutrophil
Interstitium
Macrophage
CD4 T cell
Tregs
Dendritic cell
Tubular epithelium
Early injury phase
Adhesion molecule
Monocyte
Macrophage
NK T cell
Neutrophil
Cytokines & Chemokines
NK cell
Complement
Repair phase
Platelet
Tregs
Tregs

CONCLUSION

- Macrophages and distinct T-cell subsets are capable of anti-inflammatory as well as proinflammatory functions.
- Wound-healing macrophages (M2a) , regulatory macrophages (M2c) and regulatory T cells (Tregs) are remarkably potent at reducing renal injury in a number of different renal disease models.
- Understanding the biology of macrophages and lymphocytes and their ability to repair renal tissue will enable the future discovery of therapies for kidney diseases.


Thank you